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RELATION BETWEEN ELECTROENCEPHALOGRAPHIC AND HISTOLOGIC CHANGES FOLLOWING THE APPLICATION OF GRADED FORCE TO THE CORTEX

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THE electroencephalographic effects of trauma to the brain have been studied by a number of investigators. Williams and Denny-Brown,[1] among others, have shown that a pathologic condition is indicated by the presence of slow waves of increased amplitude following a blow on the skull. These effects were produced experimentally on cats.

The pathologic changes in the various cytologic elements following injury to the brain have also been studied by a number of investigators. The recent work of Rand and Courville describes in detail such histologic changes.[2]

The present experiments were designed to investigate the possible relationship between the electroencephalographic patterns and the histopathologic changes occurring simultaneously after the application of graded force to the cortex. In order to investigate these changes a specially designed apparatus was used.

MATERIALS AND METHODS

Apparatus.—The traumatizing element (fig. 1 *A* and *B*) consists of an electromagnet with a hinged armature tuned to 60 cycles, alternating current. Mounted on the armature is a bent lucite (methyl methacrylate) rod which strikes the cortex when the armature is attracted by the electromagnet. The traumatizing element is also attached to a fine adjustment mechanism, and both are rigidly mounted to the center of a round bar ½ inch (1.27 cm.) in diameter and 16 inches (40 cm.) in length. Mounted on an animal board on each side are two double upright, rectangular rods. The round bar is held in place by two wing nuts on each double rod.

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1. Williams, D., and Denny-Brown, D.: Cerebral Electrical Changes in Experimental Concussion, Brain **64**:223, 1941.

2. Rand, C. W., and Courville, C. B.: Histologic Changes in the Brain in Cases of Fatal Injury to the Head: VII. Alterations in Nerve Cells, Arch. Neurol. & Psychiat. **55**:79 (Feb.) 1946.

This permits adjustment in a vertical plane. The round bar also serves as an axis around which the traumatizer can be rotated. The entire set-up permits universal adjustment of the traumatizer in any plane.

The control electrodes have dimensions identical with the experimental electrodes and are embedded in a straight lucite rod, which is slightly smaller in diameter than the trephine hole. This lucite rod is held in position in a clamping

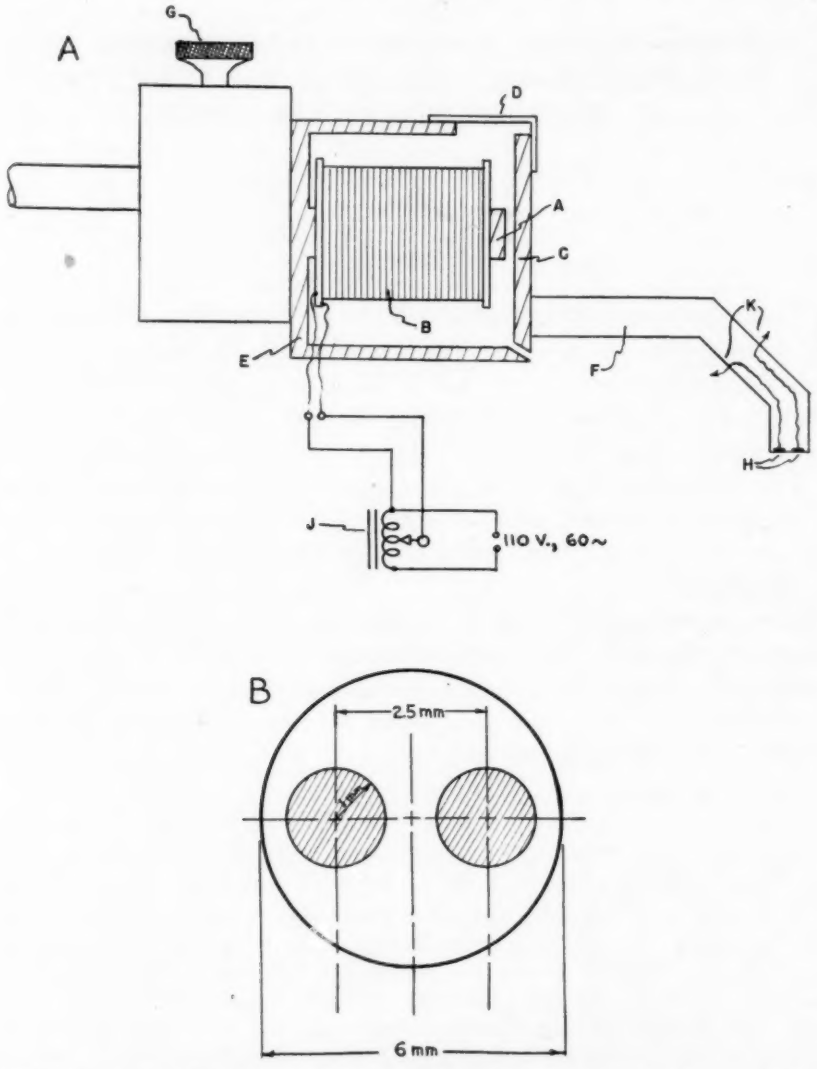

Fig. 1.—*A*, profile diagram of traumatizing element in its circuit. *A*, indicates core; *B*, coil; *C*, vibrating armature; *D*, flat spring brass; *E*, yoke; *F*, lucite rod; *G*, micrometer feed screw; *H*, silver disk electrodes; *J*, variable autotransformer, and *K*, flexible leads to panel board.

B, end view of traumatizing rod. The lucite traumatizing rod is 6 mm. in diameter. Two silver disk electrodes, 2 mm. in diameter, spaced 2.5 mm. on center, are sunk flush with the face of the rod.

collar with set screw. The collar is attached to a universal ball joint clamped rigidly to the round bar.

Method.—One hundred and ninety-five experiments were made on cats, which were selected on the basis of weight and age. All the cats were approximately of the same age, and each weighed about 5 pounds (2.3 Kg.). Pentobarbital sodium was used as an anesthetic and was administered intraperitoneally. The animal was placed on a stand with all four extremities freely movable; the head was firmly held in a head holder. The skull was trephined bilaterally. The burr holes were always placed to secure exposure of the middle suprasylvian gyrus just anterior to its juncture with the posterior suprasylvian gyrus, in the posterior part of the parietal lobe. The dura was always left intact.

The traumatizing rod was lowered with the fine adjustment screw until its face was lightly touching and exactly astride the middle suprasylvian gyrus. The control rod, on the contralateral side, fitted snugly in the burr hole and was likewise lowered until it was just flush with the dura.

The preparation on its stand, the switches and the panel board for the electrodes were placed in a shielded, grounded cage. A Grass three channel, ink-writing oscillograph was used for recording.

The voltage, and therefore the force applied, was varied with an autotransformer connected directly to the electromagnet. Voltages of 50, 85, 100 and 120 volts, respectively, were used, representing a range in force from a barely perceptible vibratory sensation, at 50 volts, to a 6 mm. excursion of the traumatizing hammer, at 120 volts. The time of application varied from three to twenty seconds for each of the voltage categories. A stopwatch was used in varying the duration of the force applied to the cortex.

Bipolar and monopolar potentials were recorded simultaneously on the experimental side. Bipolar potentials only were recorded on the control side.

The electroencephalographic potentials were recorded almost immediately after the application of the force to the cortex, and from the exact area traumatized. Five seconds, on the average, elapsed between the end of trauma and the start of recording. The potentials were recorded through the dura for forty-five minutes following traumatization. A second recording was made on each preparation four days later. The animal was killed immediately after the end of the four day recording. The traumatized areas were marked with a cork borer of the same size as the electrode-bearing rods. A slight indentation just sufficient for subsequent localization was made in the cortex after the dura had been removed.

The brain was immediately fixed in neutral solution of formaldehyde U. S. P. (1:4). A coronal section through the plane of the traumatized and control areas was subsequently made. The sections were stained with cresyl violet.

RESULTS

Electroencephalographic Changes.—As previously stated, traumatizing activity was recorded in terms of voltage (intensity of force) and the duration of the force applied.

The amount of electroencephalographic change was classified under four categories, viz., pronounced, moderate, mild and none, depending on the reduction in amplitude and the presence of slow waves.

Normal, or base line, activity in the narcotized (pentobarbital) cats consists of bursts, each lasting several seconds, of potentials occurring at a rate of 8 to 10 per second and recurring every two or three seconds. Between the bursts, low voltage, irregular activity is seen.

The deviations from the normal base line activity seen in these experiments were reduction in amplitude of varying degree, with loss of superimposed fast activity in the presence of delta waves of varying frequency, amplitude and form, and change in the amplitude and frequency of the pentobarbital spikes.

It will be noted that the intensity and duration of the force applied (fig. 2) produced no apparent electrical change in the categories below

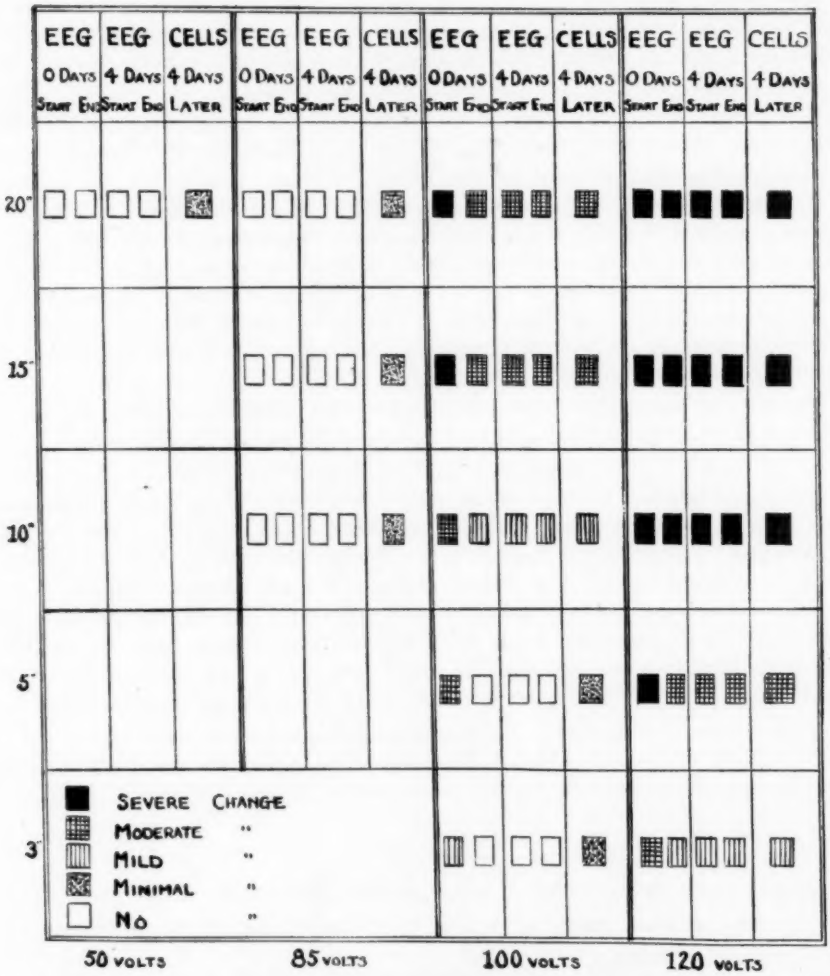

Fig. 2.—Degree of electroencephalographic change immediately after trauma, forty-five minutes later and four days later, and the degree of histologic change four days later, in relation to the intensity and duration of the force applied.

the 100 volt, three second interval. Above this level the electrical changes varied with the intensity and duration of the force applied. The most pronounced changes occurred at the 120 volt level between the ten and the twenty second interval.

Figure 3 represents the most pronounced type of electrical change. The first and third tracings in all figures represent bipolar and monopolar leads, respectively, from the experimental side. The middle tracing represents the contralateral (control) side, recorded with a bipolar lead. In figure 3 *A*, taken with the animal under moderately

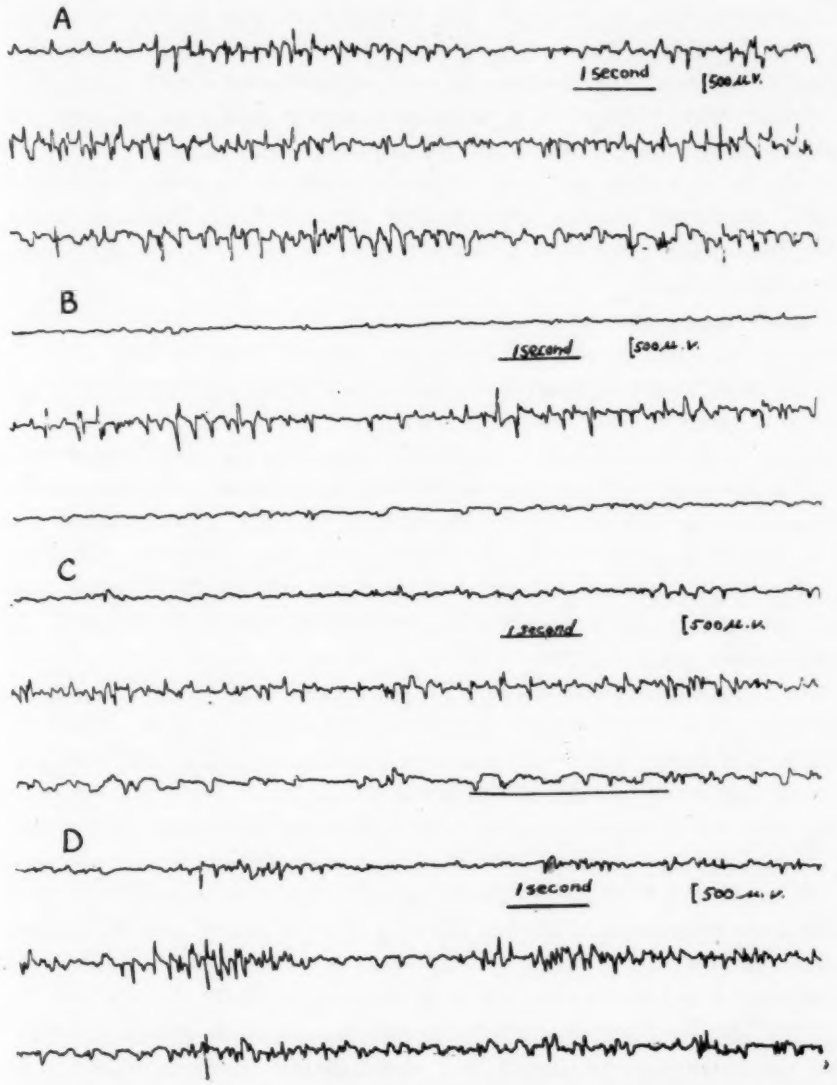

Fig. 3.—Severe electrical change following traumatization of the cortex. The base line activity, immediate changes and changes forty-five minutes and four days after traumatization are shown in *A*, *B*, *C* and *D*, respectively. The first and third tracings in this figure, and in figures 4 to 8, represent the bipolar and the monopolar recording, respectively, from the traumatized area; the middle tracing is a bipolar recording from the corresponding contralateral area. Note the marked reduction in amplitude in leads I and III immediately after trauma and the run of high voltage, slow waves in lead III forty-five minutes after trauma. For details see text.

deep barbiturate (pentobarbital) anesthesia, normal base line activity is seen. Immediately after trauma (fig. 3 *B*) there is a striking reduction in electrical activity in leads I and III with a suggestion of low voltage, flat-topped waves in the monopolar (third) lead. The middle tracing, from the control side, shows some loss in superimposed fast activity and a general slight reduction in amplitude. At the end of forty-five minutes (fig. 3 *C*) a little low voltage, irregular activity is apparent in lead I, with a bare suggestion of barbiturate bursts beginning to appear. In lead III there is an almost continuous run of somewhat irregular, high voltage, slow waves, occurring at a rate of 2 to 3 per second. Most of these waves are flat topped. Four days later (fig. 3 *D*) the bipolar recording in lead I shows distinct low voltage pentobarbital bursts appearing between stretches of inconspicuous electrical activity. The monopolar (third) lead shows some irregular, flat-topped waves between the bursts.

Moderate electrical changes are represented in figure 4. These changes occurred in the 120 volt, five second category (fig. 2). The tracing from lead I in figure 4 *B*, taken immediately after trauma, is again almost a straight line, but with some superimposed, inconspicuous low voltage, irregular activity. Lead II, representing the corresponding area of the contralateral side, shows the same pattern as that described in lead II, figure 3 *B*. In the third, or monopolar, tracing some irregular, high voltage, 2 to 3 per second waves are apparent. This is in contrast to the marked reduction of electrical activity in the corresponding tracing (fig. 3 *B*) representing pronounced electrical changes. The single spikes are artefacts.

After forty-five minutes (fig. 4 *C*) a considerable return of alternating differences in potential is apparent in the bipolar tracing, represented by the first line. The tracing shows abortive pentobarbital bursts and low voltage, irregular activity between the bursts. High voltage, irregular, slow (3 to 4 per second) waves continue to appear in the third, or monopolar, experimental tracing. Some of the latter potentials have a tendency to be roughly square topped. Four days later (fig. 4 *D*) the bipolar experimental tracing shows 2 to 3 per second, medium voltage waves interspersed between similar abortive pentobarbital spikes. The monopolar third lead again approximates more nearly the normal.

Mild electrical changes following trauma are represented in figure 5. The three tracings in figure 5 *A* indicate the usual base line. The experimental bipolar recording immediately following trauma, represented by the first tracing in figure 5 *B*, shows a general, though less prominent, reduction in amplitude with abolition of the pentobarbital spikes. The amount of activity is quite similar to that seen forty-five minutes after severe trauma, shown in the first tracing of figure 3 *C*. In the third tracing (fig. 5 *B*) the irregular, 3 to 4 per second, high

voltage waves appear immediately. The slow waves just mentioned are apparently of lower potential than those seen forty-five minutes after severe trauma (fig. 3 *C*).

In comparing the first tracing of figure 5 *C* with the corresponding base line, there is, apparently, considerable return of electrical activity

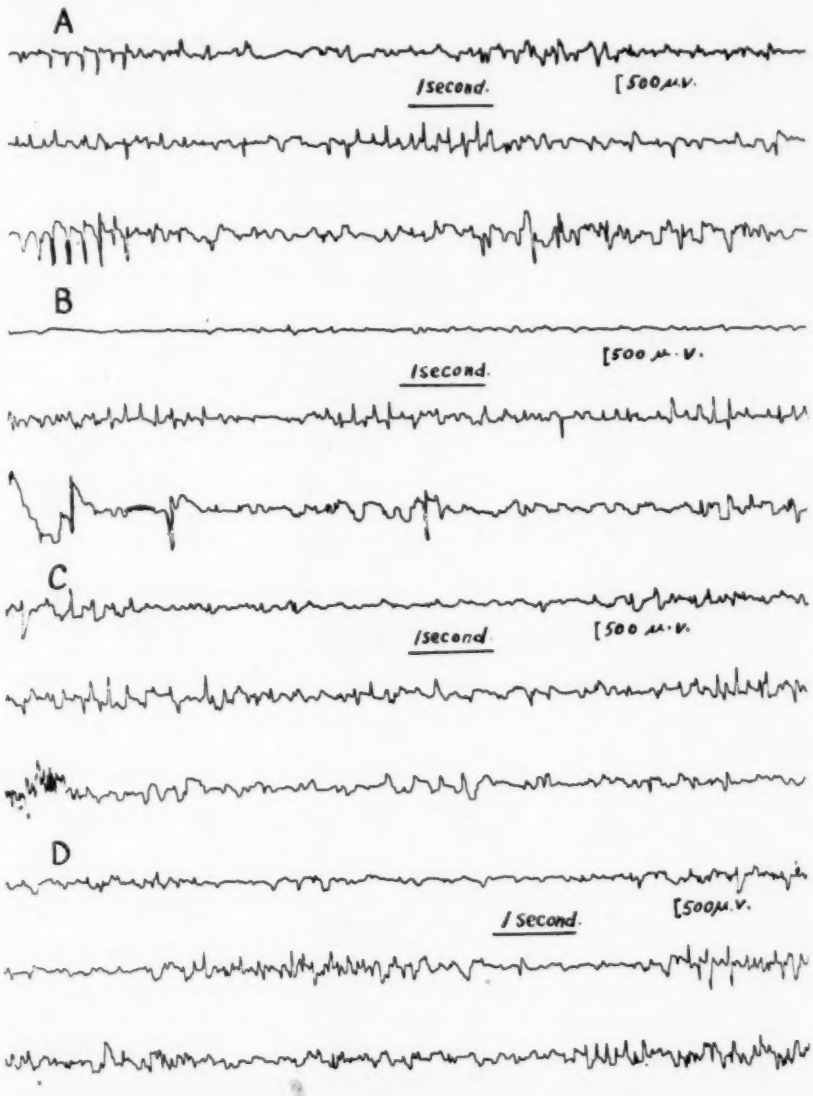

Fig. 4.—Moderate electrical change following traumatization of the cortex. Note the reduction in amplitude in bipolar lead I and the immediate appearance of irregular slow waves in lead III following trauma, in contrast to the later appearance of slow waves shown in figure 3.

forty-five minutes after trauma. The pentobarbital bursts are distinct, although somewhat reduced in amplitude. Medium voltage, slow waves also occur intermittently between the pentobarbital bursts.

Four days later (fig. 5 *D*) the experimental bipolar tracing (lead I) is practically unchanged, although the occasional medium voltage, slow waves seen forty-five minutes after trauma are not shown in the tracing. The monopolar experimental recordings, both forty-five minutes and four days later, are practically unchanged.

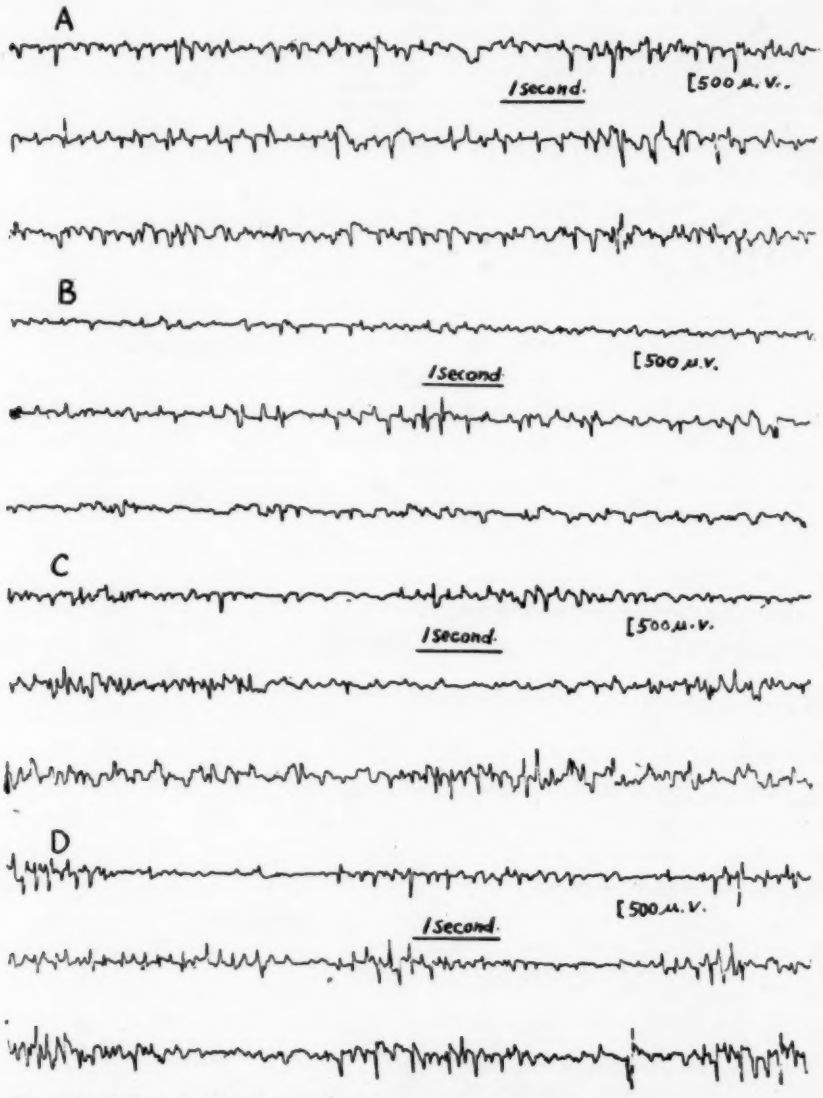

Fig. 5.—Mild electrical change following traumatization of the cortex. Note the less prominent reduction in amplitude in lead I and the continued presence of slow waves in lead III immediately following trauma. For details see text.

It can be seen from figure 2 that in the presence of a normal electroencephalogram minimal histologic changes occurred. Figure 6 represents a tracing recorded after delivering a force represented by 50 volts

for twenty seconds to the cortex. The tracing shows no changes in any of the three recording periods.

Figure 7 represents the same type of recording in a sham experiment. No trauma was applied to the cortex. The tracings in figure 7 *B* were taken after forty-five minutes; those in figure 7 *C* were taken four days later. There is no apparent change.

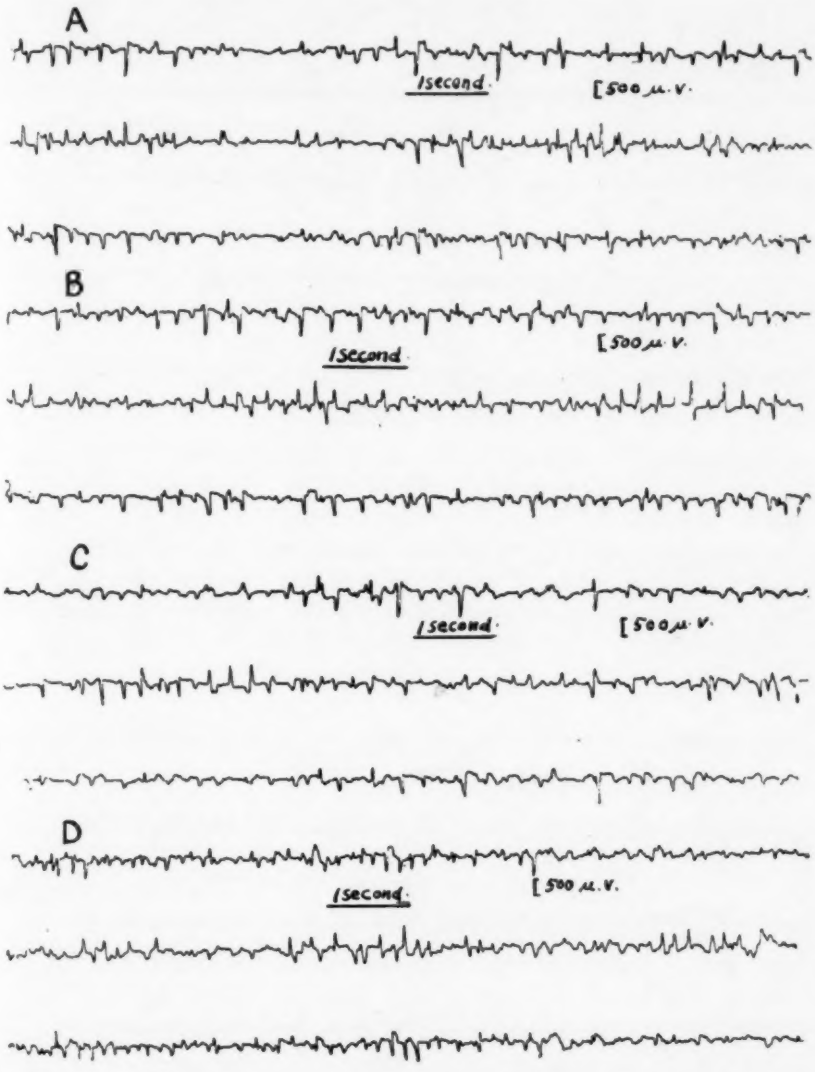

Fig. 6.—Unchanged electrical activity associated with minimal cortical cell damage.

At times it was noted that convulsive patterns were produced when a force equivalent to 120 volts and lasting for twenty seconds was applied to the cortex. These patterns were not always accompanied with convulsive movements. Figure 8 represents a convulsive pattern

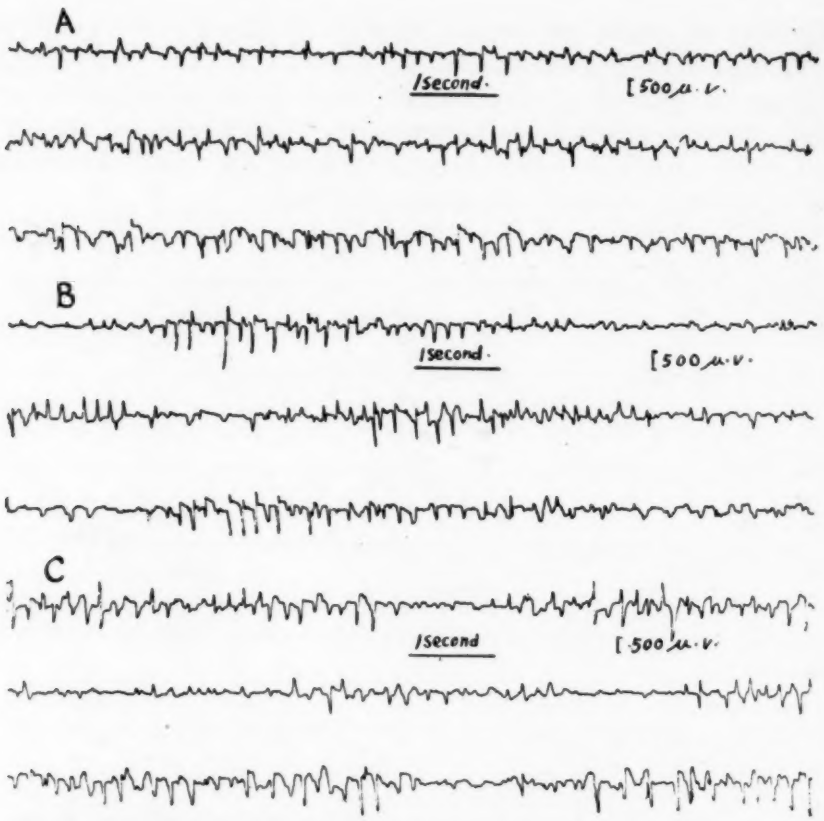

Fig. 7.—Electrical activity observed in a sham experiment at the beginning (*A*) and the end (*B*) of a forty-five minute period and four days later (*C*).

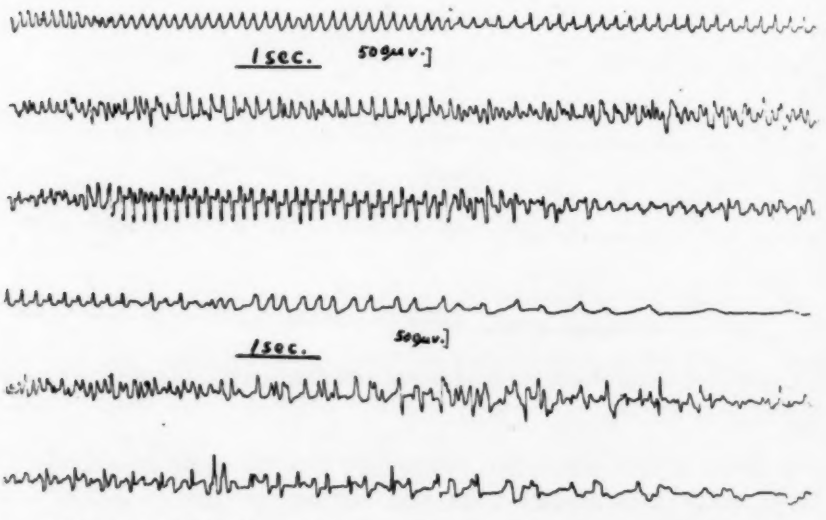

Fig. 8.—Unilateral convulsive pattern produced by traumatization.

recorded immediately after the cessation of trauma. It was not accompanied with convulsive movements. The animal was under rather light anesthesia. Eight per second spikes are seen in both lead I and lead III but are of less amplitude in the bipolar lead I. In the monopolar lead III it can also be seen that the spike formation gradually tapers off into irregular spike and wave formations. The convulsive pattern is likewise confined to the experimentally traumatized side and does not spread to the contralateral (control) side, although the number of single spikes in the early recording on the control side would appear to indicate some irritability of cells on that side.

Histologic Changes.—The histologic changes observed in connection with the previously mentioned categories of electrical change were outstanding in terms of extent and degree of cortical cell damage. The traumatized area could be distinguished easily from the surrounding tissue under the low power lens by its pallid appearance.

The greatest amount of cell damage occurred when a force represented by 120 volts, with a duration ranging from ten to twenty seconds, was applied. The detailed histologic changes seen four days after trauma are shown in figure 9. Under the low power lens, as seen in the upper figure, the traumatized area stands out in sharp relief by virtue of a clearly delineated area of pallor involving all cortical layers. This area of pallor mushrooms out somewhat from the point of impact, as can be seen in this figure. The photomicrograph was taken slightly to the left of the area of greatest damage, which is most obvious along the right hand margin. The normal architectonic arrangement of the cells is disrupted; the cells appear strewn about in a capricious manner, and the field presents a general wind-swept appearance. A reduction in the number of cells is apparent in all layers. Bare areas and shadow-like cells are striking. The cells in the second layer, as can be seen in the lower left portion of figure 9, are swollen, and the margins of many have a "chewed-out" appearance. The pericellular spaces are notably enlarged in many instances. In the same figure, vacuolation and segmentation of the cells are also suggested.

The large pyramidal cells (lower right portion, fig. 9) are in most instances pale, with hazy, indistinct and irregular margins. The nucleus as a rule is eccentrically placed, often lying against the cell membrane, sometimes jutting into it, as though about to extrude into the surrounding medium. The nuclear margins are not sharply outlined but appear irregular and in folds; the nucleus, consequently, is somewhat shrunken. The aforementioned changes are similar to those described by other investigators and have been attributed to the direct effect of trauma, i. e., the shock of injury to the cortex combined with a disturbance of

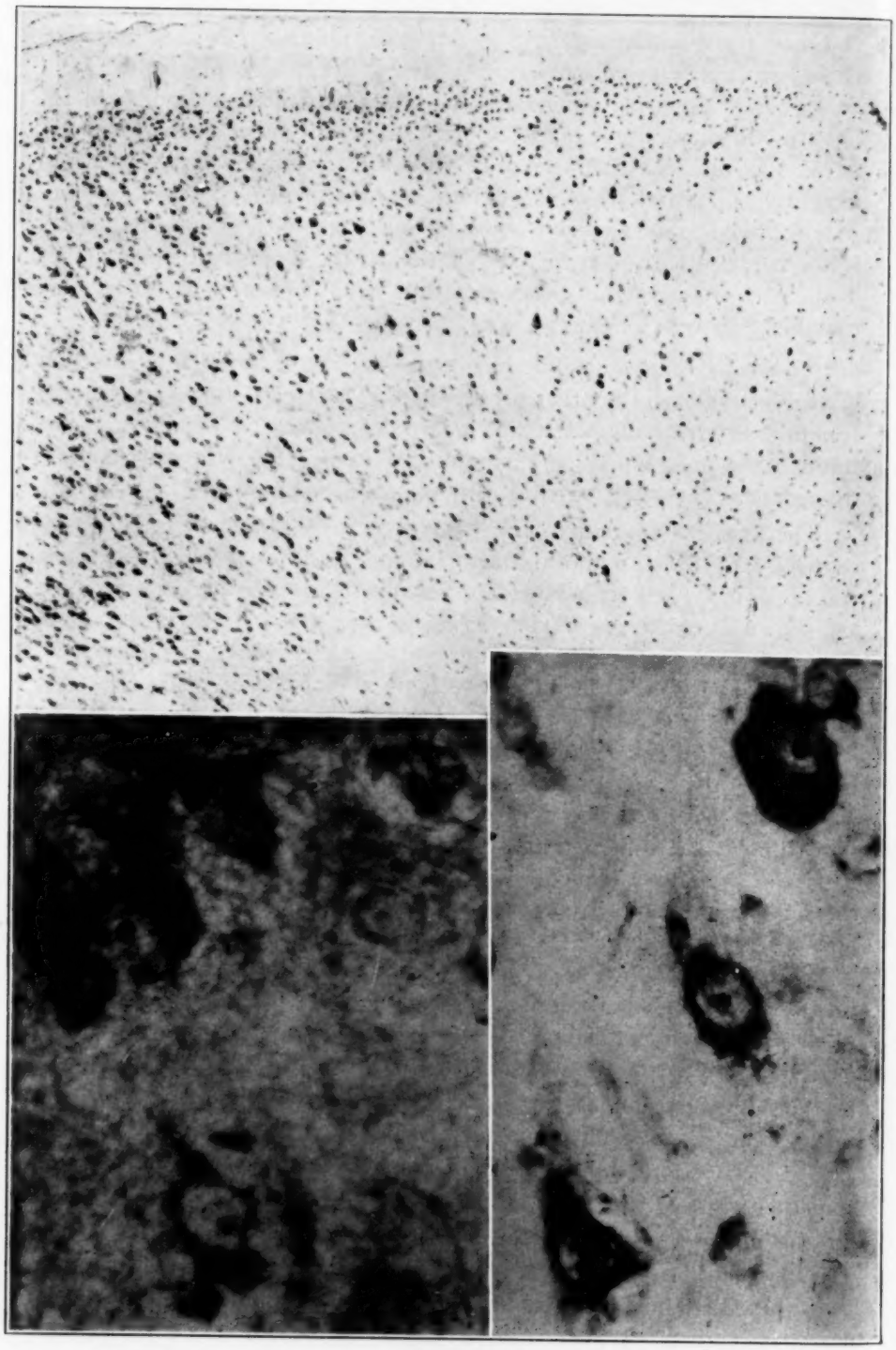

Figure 9

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the fluid balance in the cerebral tissues. Scagliosi [3] studied the histologic effect of striking a series of animals on the head with a hammer and observed that after twenty-four hours the cell had lost its granular substance and assumed a pale blue, homogeneous appearance. Büdinger [4] also noted a tendency of the cells to lose their staining capacity. Jakob [5] observed eccentration of the nucleus in the cells of the cerebral cortex, swelling and early chromatolysis. Windle, Groat and Fox [6] produced concussion by striking the movable head of the guinea pig and demonstrated that the Nissl bodies were disorganized, some being fragmented and others agglutinated, and that the normal pattern and arrangement of such bodies were significantly changed. Rand and Courville [2] stated that "the shocking effect of the injury appears to be responsible for loss of the tigroid substance from the cell . . .; [and] shrinkage of the nucleus, with the assumption of an irregular shape and the formation of folds in the nuclear membrane." These authors concluded that the cell changes may be general, as a result of the shock of the traumatizing force, or consequent to the general edema, with vacuolation, and emphasized the alterations directely resulting from focal injuries to the cortex.

Cellular changes designated as moderate damage are shown in figure 10. Under low magnification (upper figure) the traumatized area is not so sharply delineated from the surrounding cortical tissue.

3. Scagliosi, G.: Ueber die Gehirnerschütterung und die daraus im Gehirn und Rückenmark hervorgerufen histologische Veränderungen, Virchows Arch. f. path. Anat. **152**:487, 1898.

4. Büdinger, K.: Ein Beitrag zu der Lehre von der Gehirnschütterung, Deutsche Ztschr. f. Chir. **41**:433, 1895.

5. Jakob, A.: Experimentelle Untersuchungen über die traumatischen Schädigungen des Zentralnervensystems (mit besonderer Berücksichtigung der Commotio cerebri und Kommotionsneurose), in Nissl, A., and Alzheimer, F.: Histologie und Histopathologie Arbeiten über die Grosshirnrinde, mit besonderer Berücksichtigung der pathologischen Anatomie der Geisteskrankheiten, Jena, G. Fischer, 1913, vol. 5.

6. Windle, W. F.; Groat, R. A., and Fox, C. A.: Experimental Structural Alterations in the Brain During and After Concussion, Surg., Gynec. & Obst. **79**: 561, 1944.

Fig. 9.—Severe cortical cell change.

Upper figure (magnification, 60), uniform cell pallor involving all cortical layers. The photograph was taken slightly to the left of the traumatized area to show the mushrooming extension of the lesion.

Lower left figure (magnification, 560), cells from the second cortical layer, showing swelling, "chewed-out" appearance of the margins and segmentation. The cell in the center of the lower margin, in addition, shows enlargement of the pericellular space.

Lower right figure (magnification, 560), eccentration of the nucleus of a pyramidal cell.

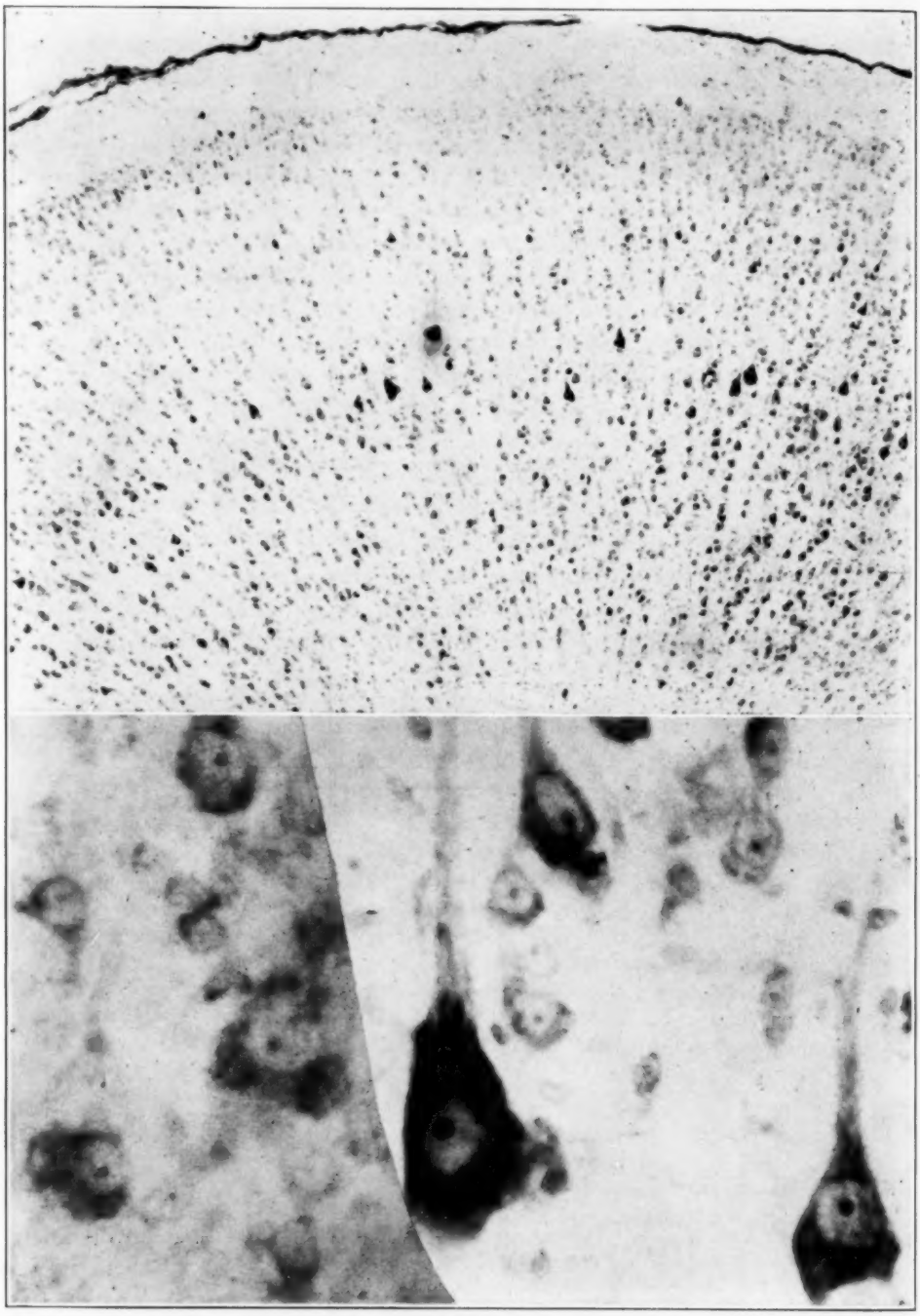

Figure 10

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The field presents a stippled appearance, especially in the deeper layers. Osnato and Giliberti [7] also noted an unevenness in the staining qualities of the cortex following injuries to the human brain. The cell pallor, which involves all cortical layers in severe damage, is here most marked in the second layer and the outer portion of the third layer. The cells are still swollen, very pale and indistinct and have the same "chewed-out" appearance (lower left portion, fig. 10). The cellular disarrangement is likewise most marked in the aforementioned layers; below that the disturbance in position of the cells is milder.

Some of the large pyramidal cells are fairly normal in appearance (lower right portion, fig. 10), and their deeper stain largely gives the stippled quality to the field. Other large pyramidal cells which were damaged were moderately pale with irregular margins, but the nucleus was not usually eccentrated.

Mild cellular change is exemplified in figure 11. Under the low power lens (upper figure) the changes are seen to be predominantly in the internal granular layer, with a shading off in severity of cell damage above and below this layer. Architectonic disarrangement, paucity and pallor of cells are still apparent.

The external granular layer is more normal in appearance, and reduction in the number of cells is not so marked but some of the cells show varying degrees of pallor and appear slightly swollen (lower portion, fig. 11).

With minimal cell damage, observed with a normal electroencephalogram, there is no apparent reduction in the number of cells (upper portion, fig. 12). A few pale cells are seen in the third, fourth and fifth cortical layers. A few pyramidal cells also appear somewhat pale (lower right portion, fig. 12), but the majority are normal in appearance. The cells in the second layer are not disarranged, and the apical dendrites point normally toward the surface of the cortex (lower left portion, fig. 12).

7. Osnato, M., and Giliberti, V.: Postconcussion Neurosis: Traumatic Encephalitis; a Conception of Postconcussion Phenomena, Arch. Neurol. & Psychiat. **18:** 181 (Aug.) 1927.

Fig. 10.—Moderate cortical cell change.

Upper figure (magnification, 60), damage, as indicated by cell pallor, most pronounced in the second and third layers.

Lower left figure (magnification, 560), swollen, pale and indistinct cells of the second cortical layer.

Lower right figure (magnification, 560), fairly normal large pyramidal cells, contributing to the stippled appearance of the field.

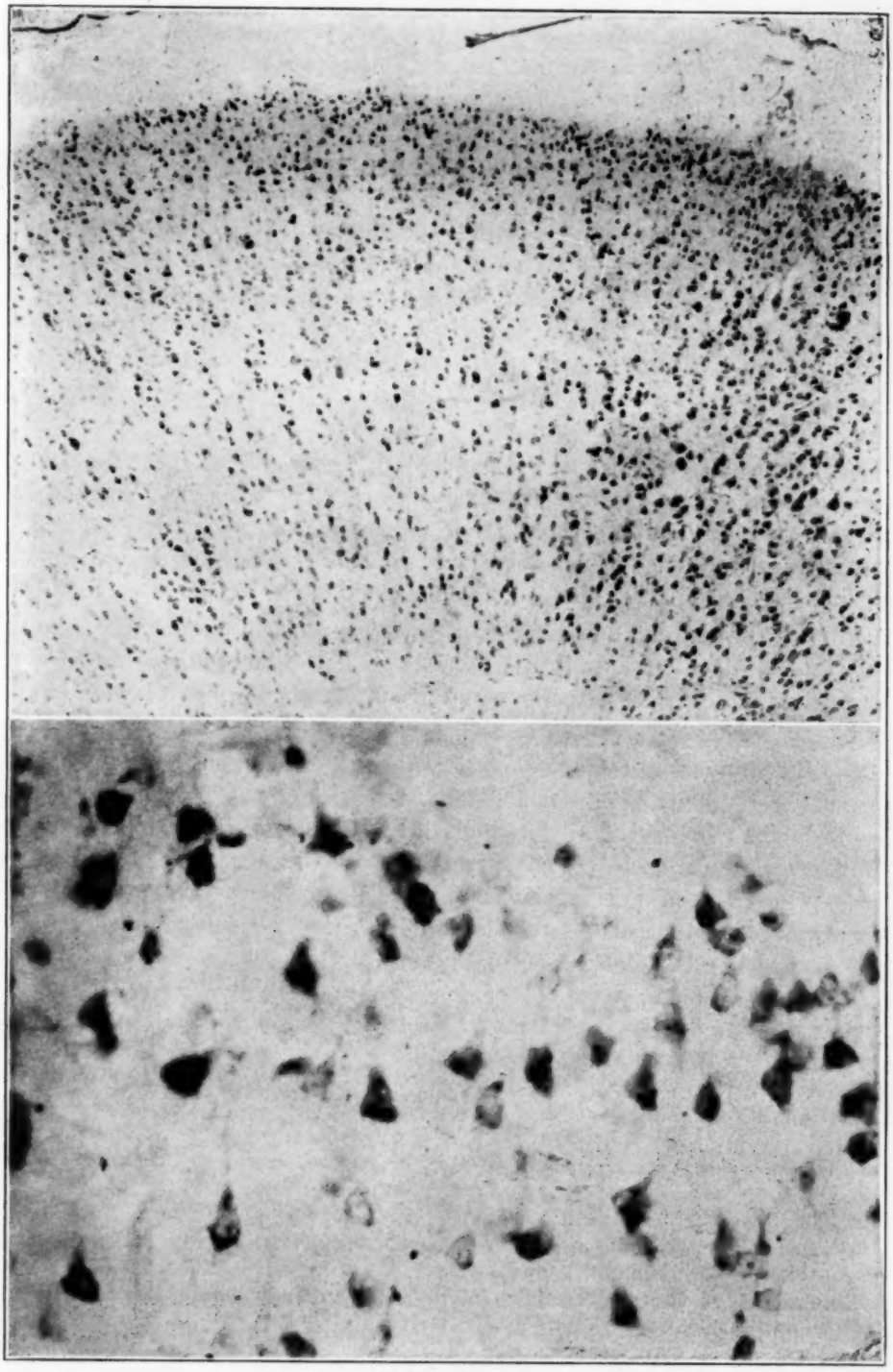

Figure 11

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Figure 13 illustrates the normal appearance of the cortex following a sham experiment. The general experimental procedure was followed, but without the application of trauma to the cortex.

The histologic picture from the contralateral (control) side invariably revealed slight cell changes when the force applied on the experimental side was sufficient to produce electrical change. The changes, however, were never more than minimal in degree.

In order to investigate the early cell changes following trauma to the cortex, especially in their relation to early electrical changes, an animal was killed at the end of a forty-five minute period of electroencephalographic recording. In this experiment a force equivalent to 100 volts lasting twenty seconds was delivered to the cortex. Figure 14 (upper portion) shows a multiplication of glial elements. This reactive phenomenon is predominantly in the form of a diffuse satellitosis involving the upper three cortical layers. Below these layers the satellitosis is more scattered. In the large pyramidal layer not all the Betz cells are equally affected. In general, satellitosis in this layer is most conspicuous around giant cells, which appear homogeneous, in contrast to cells showing a greater differentiation of the cellular elements. The distribution of this acute cell picture in terms of the cortical layers involved is similar to that seen with moderate cell changes four days later (fig. 10). In the lower, high power, view the glial elements can be seen to consist of oligodendrocytes, microgliocytes and swollen astrocytes.

Relation Between Electroencephalographic and Histologic Changes.—The electroencephalographic and the histologic changes are tabulated in terms of intensity and duration of force in figure 2. The extent and degree of cortical cell change at the four day period associated with the corresponding electrical changes for the same period are likewise recorded. The electrical changes are classified as pronounced, moderate, mild and none, in terms of the degree of diminution of electrical activity subsequent to the delivery of the particular force to the cortex.

It will be seen in figure 2 that at the 50 and 85 volt levels histologic changes occurred without corresponding electrical changes in the respective time categories. This would seem to indicate that abnormal electrical changes depend on the number and type of cells damaged. The variability of change in certain cells may be an added factor. Rand

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Fig. 11.—Mild cortical damage.

Upper figure (magnification, 60), cell pallor, involving predominantly the internal granular layer, with shading off in severity of damage in the layers above and below.

Lower figure (magnification, 190), cells from the second cortical layer, showing varying degrees of pallor and slight swelling.

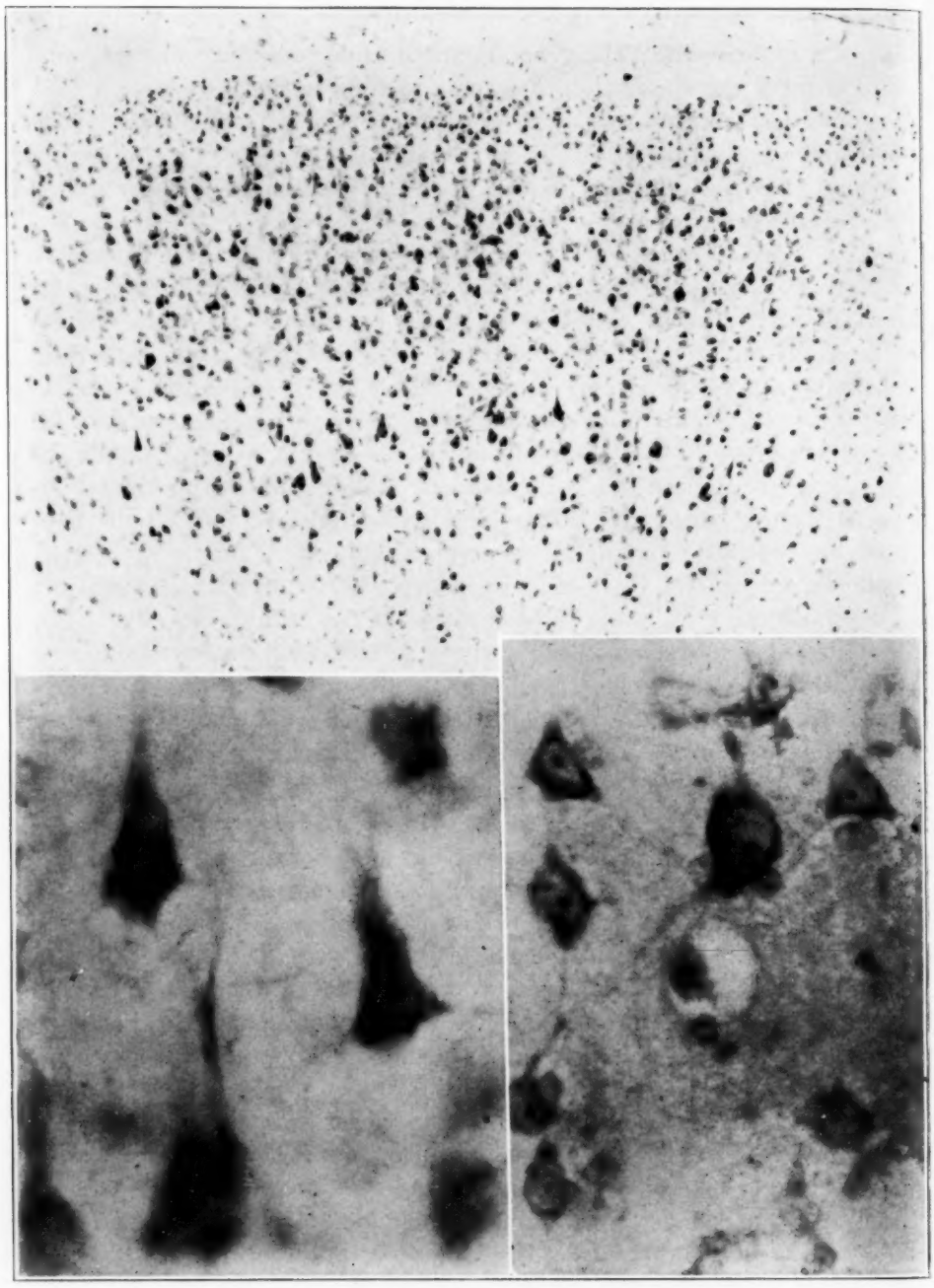

Fig. 12.—Minimal cortical cell change, seen in connection with a normal electroencephalogram.

Upper figure (magnification, 60), scattered, irregular distribution of cell pallor of varying degree.

Lower left figure (magnification, 560), cells of the second layer, showing normal polarity of the dendrites with the surface of the cortex.

Lower right figure (magnification, 560), pale cells in the third cortical layer.

and Courville [2] at the end of six days observed cells which showed only slight chromatolytic changes and concluded that there was a variability in the "rapidity of loss of tigroid substance." They also expressed the opinion that, among other factors, the "degree of shock of the original injury" accounted for some of the variability.

The degree of shock, the number and type of cells injured and their capacity to resume their normal function would seem to determine not only the degree of electroencephalographic abnormality but also the rapidity with which it returns to normal. There is some evidence in this direction in the electrical and histologic changes indicated in the

Fig. 13.—Cortical cells from sham experiment; magnification, 60.

100 volt, 3 and 5 second categories shown in figure 2. Immediate electroencephalographic changes are seen which return to normal within forty-five minutes, but which are associated with minimal cell changes at the end of the four day period. This is in contrast to the more persistent electrical changes associated with greater cell damage following greater increments of force.

Similar factors might be the basis of the normal electroencephalograms observed at times in connection with clinical signs of concussion in man. Jasper, Kershman and Elvidge [8] reported 16 cases in which the patients

8. Jasper, H. H.; Kershman, J., and Elvidge, A. R.: Electroencephalography in Head Injury, A. Research Nerv. & Ment. Dis., Proc. (1943) **24**:388, 1945.

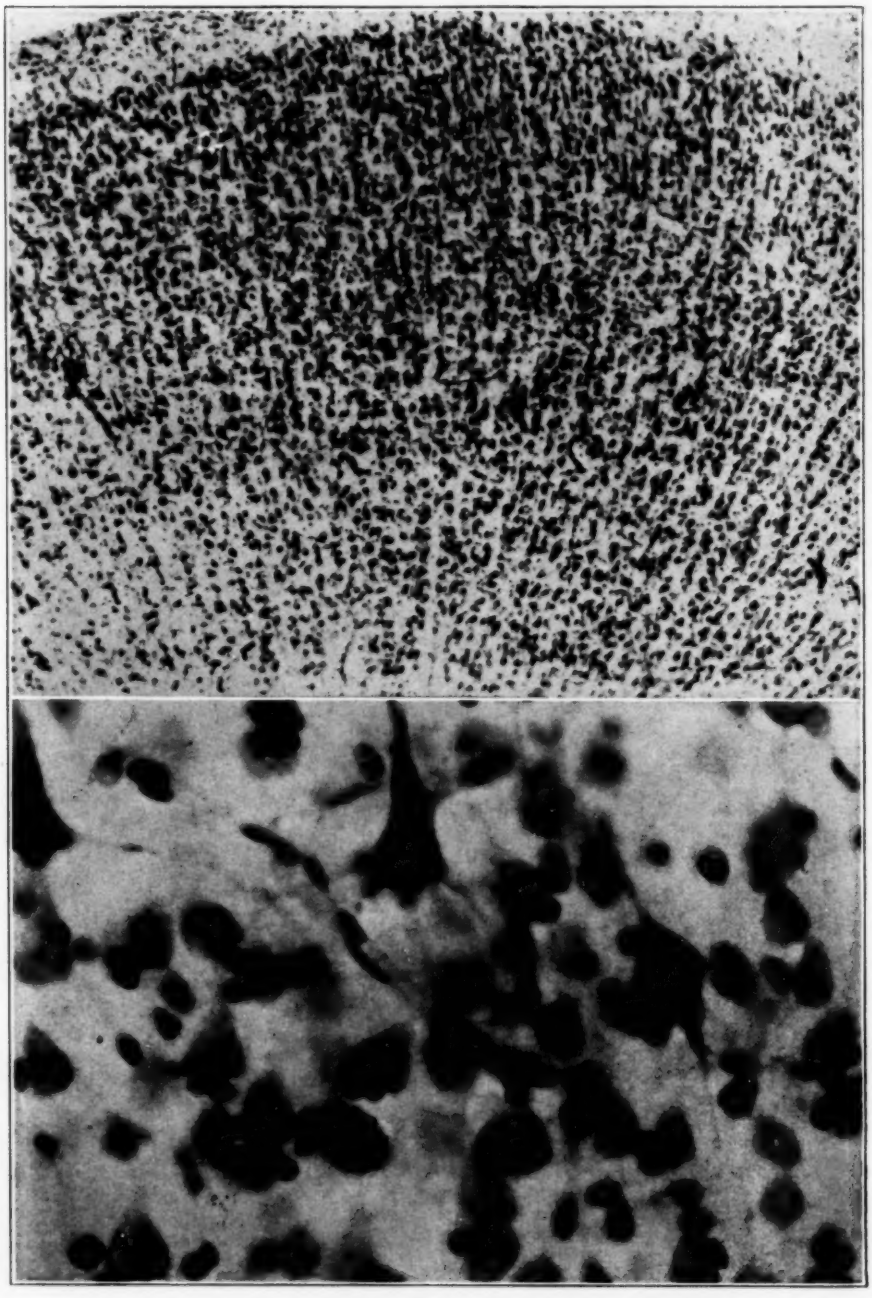

Fig. 14.—Traumatized cortex forty-five minutes after severe trauma.

Upper figure (magnification, 60), multiplication of glial elements in the traumatized area.

Lower figure (magnification, 540), details of reactive gliosis, with presence of microglia cells, oligodendrocytes and astrocytes.

had normal electroencephalograms despite a history of loss of consciousness of from eleven to sixty minutes. Similar findings have been reported by Williams [9] and by Dow, Ulett and Raaf.[10] The latter authors cited a case in which the electroencephalogram was normal within fifteen minutes after the patient sustained a true concussion, as judged by clinical symptoms.

Above the 100 volt, five second level, it will be seen that the degree of histologic and electrical change at the end of the four day period varies with the intensity and duration of the force delivered to the cortex. In addition, the degree of diminution of potential and the amount of reversibility at the end of forty-five minutes in the respective categories appear to be functions of the same force. It is also evident from figure 2 that the capacity to recover, as indicated by the electroencephalographic patterns, is greater within the initial forty-five minute period than after the four day period.

The most pronounced electroencephalographic and histologic changes resulted from the application of a force equivalent to 120 volts within a time range of ten to twenty seconds. A comparison of the four day electroencephalographic record with the corresponding histologic picture shows that the large reduction in amplitude is associated with the most widespread histologic damage, involving all cortical layers.

In comparing the cell changes (fig. 14) occurring forty-five minutes after application of a force of 120 volts for twenty seconds with the corresponding electroencephalographic tracing (fig. 3 *C*), it is seen that the reduced amplitude and high voltage, slow waves occur in the presence of acute cell changes. The multiplication of glial elements is in striking contrast to the histologic changes occurring four days later. The predominance of slow waves within the forty-five minute period, as against their paucity four days later, and the presence of slow waves in association with a picture of acute cell damage, suggest that the slow waves represent either an effort at, or a stage in, recovery. These observations appear to be in conformity with the direct experimental observations on the electroencephalographic changes following head injury made by Williams and Denny-Brown,[1] who produced cerebral concussion in cats under light pentobarbital and ether anesthesia. They found that concussion was always associated with diminution or cessation of electrical activity and the appearance of abnormally slow waves. In our method of recording, however, with simultaneous bipolar and monopolar tracings from the experimental area, these two effects seem to arise from different

9. Williams, D.: The Electroencephalogram in Acute Head Injuries, J. Neurol. & Psychiat. **4**:107, 1941.

10. Dow, R. S.; Ulett, G., and Raaf, J.: Electroencephalographic Studies Immediately Following Head Injury, read at the Ninety-Ninth Annual Meeting of the American Psychiatric Association, Detroit, May 10-13, 1943.

levels, with the inference that the delta waves have a deeper origin, since, according to Jasper and associates,[11] the monopolar type of recording picks up activity from deeper intracranial structures than does the bipolar method. We were unable to demonstrate cellular changes in the subcortical structures within the limits of the degrees of force applied.

It is also of interest to point out that the type of tracing seen in figure 3 *C*, with diminished electrical activity in the bipolar recording and simultaneous delta waves in the monopolar tracing, is similar to that described by Jasper, Kershman and Elvidge [12] in recording over extracerebral hematomas. These investigators found a silent area with bipolar recordings and variable delta waves in monopolar records over the same area.

The potentials from the silent area, as exemplified by diminished electrical activity, might presumably arise from the superficial cortical layers. In our experiments, in the categories of pronounced and moderate changes in the electroencephalogram, the cells in these layers, especially the second and the outer portion of the third layer, revealed changes which have been attributed by various investigators to the shock of injury or direct trauma. The diminished electrical activity, therefore, seems to arise from a physiologically silent area.

In comparing electrical and histologic changes designated as moderate (figs. 4 and 10), it may be seen that the most profound cell changes occur in the second and third cortical layers, as indicated by the extent of cell pallor. Below these layers the stippled appearance of the field indicates an irregular and variable amount and degree of cell change. While the experimental bipolar record shows immediate marked diminution of electrical activity, the monopolar experimental record, in contrast to that seen with pronounced changes, now shows irregular high voltage, slow waves which appear almost immediately after trauma. If these slow waves represent an effort on the part of the cells toward recovery, it would seem that this capacity for recovery would be greater with lesser degrees of trauma and the slow waves would consequently appear earlier.

Figure 4 *D*, representing the electrical pattern at the end of the four day period, reveals considerable return of activity as compared with the corresponding tracing seen with severe damage.

Electroencephalographic changes classified as mild are again significant by the presence of slow waves in the third lead immediately following trauma, a fairly normal pattern in the third lead forty-five minutes

11. Jasper, H. H.; Kershman, J., and Elvidge, A. R.: Electroencephalography, in Penfield, W., and Erickson, T. C.: Epilepsy and Cerebral Localization, Springfield, Ill., Charles C Thomas, Publisher, 1941, p. 380.

12. Jasper, H. H.; Kershman, J., and Elvidge, A. R.: Electroencephalographic Studies of Injury to the Head, Arch. Neurol. & Psychiat. **44**:328 (Aug.) 1940.

afterward and a persistently slight reduction of amplitude in the first lead at the end of the four day period, even though the potential represents a considerable gain over that seen just after trauma. The associated histologic changes are most prominent in the internal granular layer, with a shading off in degree of cell damage above and below this layer.

When a minimal force, represented by 50 volts and lasting twenty seconds, was applied, no electroencephalographic changes occurred at any time within the four day period (fig. 6). The corresponding, four day, histologic section (fig. 12), however, revealed minimal histologic changes scattered throughout all cortical layers. If the electroencephalogram is accepted as the physiologic indicator of underlying structural changes, it would appear that its sensitivity does not extend below a certain critical range. It seems possible, therefore, that such minimal cell changes could represent an organic substrate for the protracted psychic manifestations in those cases of head injury without subsequent clinical and laboratory abnormalities which have been designated as purely functional in nature.

COMMENT AND SUMMARY

Our experiments demonstrate that there is a direct relation between the amount and degree of cortical cell change and the degree of electroencephalographic change following trauma. This relation, however, obtains only above a level sufficient to produce incompletely reversible electrical changes. Below that level cortical cell change results without corresponding electrical change. Within the critical range the amount of electrical and cortical cell change is a function of the intensity and duration of the force applied. The histologic changes, in addition, assume a rather definite pattern. All cortical layers are conspicuously damaged in severe trauma; the second layer and the outer part of the third layer show the greatest cell change after moderate trauma, while the internal granular layer is most severely involved in mild trauma, with a shading off above and below this layer into milder cell changes.

This particular pattern of cortical cell change is similar in some respects to the changes observed by Roncali [13] in his study of the effect of compression on the cortical cells in dogs. This investigator repeated the earlier work of Neumayer,[14] who studied the cell changes in the

13. Roncali, D. B.: Intorne alle alterazioni nella fina tessitura dell'sostanza nervosa dell'encefalo conseceture delle compressione sperimentale, Arch. ed atti d. Soc. ital. di chir. **12**:144, 1898.

14. Neumayer, L.: Die histologischen Veränderungen der Grosshirnrinde bei localem Druck (Experimentalstudie aus dem histologischen Laboratorium des pathologischen Institutes zu München), Deutsche Ztschr. f. Nervenh. **8**:167, 1895-1896.

cortex of rabbits by inserting a lead shot 0.5 cm. in diameter between the dura and the calvaria and observing the histologic changes at subsequent intervals. In from ten to fifteen days Roncali observed alterations in the nerve cells of all layers and of all degrees. These alterations were similar to the cell changes observed in our experiments following severe trauma. After five days the cell changes described by Roncali were largely confined to the upper three cell layers. This distribution of cell changes is similar to that occurring in our experiments with moderate trauma. Cell changes which we described as mild would still appear to be more severe than those observed by Roncali at about the twenty-four hour period. Here, he noted beginning degeneration in the cells of the superficial layers. When, however, the differences in criteria, method and type of force applied are taken into consideration, it would appear that the histologic changes in the two experiments have much in common.

Additional evidence also emerges from our data that the degree of electrical reversibility is proportionately greater shortly after trauma than later and that this reversibility is associated with high voltage, slow waves.

With the use of simultaneous bipolar and monopolar recordings from the traumatized area, a technic of localization was utilized which seemed to indicate that the pathologically reduced potentials arise in the superficial cortical layers, while the slow waves of increased amplitude seen in monopolar recordings apparently arise from a disturbance in the deeper cortical layers.

Additional evidence that these pathologically reduced potentials arise in the superficial layers has been supplied by Dusser de Barenne and McCulloch.[15] These investigators demonstrated by laminar thermocoagulation that destruction of the outer two layers of the cortex resulted in "definite reduction in the local action potentials, from which there is some return, though they do not regain their initial size and shape at the end of one hour." Complete destruction of the outer three layers produced a marked reduction in local action potentials, with little or no evidence of return to original size and form, while destruction of the outer four layers reduced the action potentials permanently and almost completely.

The electroencephalographic abnormalities indicated are restricted to the traumatizing electrode. The recorded potentials arise from localized cerebral damage, which is responsible for the electroencephalographic abnormalities. The mild reduction in amplitude and diminution of superimposed fast activity seen at times in the contralateral tracing appear

15. Dusser de Barenne, J. G., and McCulloch, W. S.: Some Effects of Laminar Thermocoagulation upon the Local Action Potentials of the Cerebral Cortex of the Monkey, Am. J. Physiol. **114**:692, 1936.

to be the result of mechanical, contrecoup damage rather than of activity conducted across the corpus callosum. This has been demonstrated by Hoefer and Pool [16] by electrical and chemical stimulation of the cortex. These investigators demonstrated that activity from either side of the cortex is conducted along the corpus callosum, but not completely across. When they produced a unilateral (left-sided) seizure after moderately strong stimulation of the opposite (right) motor cortex, spike potentials were recorded from the right motor cortex and the corpus callosum, but not from the left motor cortex. This observation is confirmed in our experiments. When a seizure was produced (fig. 8) by mechanical stimulation of one side of the cortex, spike potentials were recorded from both the bipolar and the monopolar electrode (leads I and III) of the traumatized area, but not from the opposite side (lead II).

The experiments of Walker, Kollros and Case [17] indicate that at the moment of concussion cortical activity is increased in frequency and then decreases for a varying period, until there is little spontaneous activity. When pentobarbital was substituted as an anesthetic for vinethene and procaine, however, there was an immediate decrease in all cortical activity after trauma. This observation is identical with our electroencephalographic findings with pentobarbital anesthesia, although the greater increments of force used in some of our experiments produced a much longer period of depressed cortical activity.

Finally, our experiments indicate that the degree of reduction in electrical potential in the electroencephalogram is directly proportional to the amount of force applied to the cortex. The time of appearance of slow waves seen in connection with head injuries is inversely proportional to the amount of force delivered to the cortex.

CONCLUSIONS

A new method for the study of cortical cell change in connection with electroencephalographic deviations is introduced.

Electroencephalographic changes vary with the amount of cortical cell damage within a certain critical range.

Below this critical range cortical cell change occurs without corresponding electroencephalographic deviations.

Within the critical range the amount of electrical and cortical cell change is directly proportional to the amount of force applied to the cortex.

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16. Hoefer, P. F. A., and Pool, J. L.: Conduction of Cortical Impulses and Motor Management of Convulsive Seizures, Arch. Neurol. & Psychiat. **50**:381 (Oct.) 1943.

17. Walker, E. A.; Kollros, J. J., and Case, T. J.: Physiologic Basis of Cerebral Concussion, A. Research Nerv. & Ment. Dis., Proc. (1943) **24**:437, 1945.

Localized cortical cell damage produces localized electroencephalographic changes.

Histologic changes assume a definite pattern of stratification, according to the amount of force applied to the cortex.

Electroencephalographic changes vary with the amount of force applied to the cortex. Reduction in amplitude is directly proportional to the amount of force delivered. The appearance of slow waves is inversely proportional to the amount of force applied to the cortex.

Unilateral convulsive electrical patterns were produced by the mechanical application of force to the cortex.

An attempt is made to relate our experimental results to the clinical findings following trauma to the head.

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MALIGNANT CHORDOMA OF THE LUMBAR REGION

Report of a Case with Autopsy; Comment on Unusual Metastases to the Brain, Lungs, Pancreas, Sacrum and Axillary and Iliac Lymph Nodes

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CHORDOMA is a rarely encountered neoplasm which arises from the cell remnants of the fetal notochord. Notochordal cells are ordinarily present in the adult within the nucleus pulposus of the intervertebral disks. These cells may remain in the centers of the vertebral bodies [1] and on rare occasions may be found in the maxilla or the mandible.

Of the 266 cases recorded in the literature, the lesion was vertebral in only 36. In a small percentage of these cases the growth was in the lumbar region, and in a still smaller percentage widespread metastases occurred to distant organs. We report here a case of chordoma, surgically removed on three occasions, in which unusual metastases were finally presented. The metastases to the brain are believed to be unique.

HISTORY

When von Luschka [2] first described the chordoma its significant relation to the fetal notochord was not realized. Virchow [3] expressed belief that it was the result of degenerative cartilage. Thus, he named it "ecchondrosis physaliphora" ("ecchondrosis," from "cartilage" and "physaliphora," from "vacuole-containing cell"). However, Müller [4] apparently first advanced the idea that this tumor originates from the notochordal cells. Ribbert and Steiner [5] rather convincingly established

From the Department of Neurology and Neurosurgery, McGill University, and the Montreal Neurological Institute.

1. Richards, V., and King, O.: Chordoma, Surgery **8**:409-423, 1940.

2. von Luschka, H.: Die Alterveränderungen der Zwischenwirbelknorpel, Virchows Arch. f. path. Anat. **9**:312-327, 1855.

3. Virchow, R.: Untersuchungen über die Entwickelung des Schädelgrundes in gesunden und krankhaften Zustande und über den Einfluss derselben auf Schädelform Gesichtsbildung und Gehirnbau, Berlin, Reimer, 1857.

4. Müller, H.: Ueber das Vorkommen von Resten der Chorda dorsalis bei Menschen nach der Geburt und über ihr Verhältniss zu den Gallertgeschwülsten am Clivus, Ztschr. f. rat. Med. **2**:202-229, 1858.

5. Ribbert, M. W. H., and Steiner, H.: Ueber die Ecchondrosis physalifora spheno-occipitalis nach Untersuchungen von Hermann Steiner, Centralbl. f. allg. Path. u. path. Anat. **5**:457-461, 1894.

the origin of the chordoma by puncturing the intervertebral disk of rabbits and demonstrating that the proliferation of the herniated nucleus pulposus closely resembled histologically that of the chordoma. In 1919 Potoschnig [6] reported the first case of chordoma with widespread metastases, the tumor originating in the sacrococcygeal region.

To Klebs [7] is attributed the report of the first clinical case of chordoma which was located within the cranium. Raul and Diss [8] reported the first authentic case of vertebral chordoma in 1924. The chordoma was located in the cervical region. DesJacques [9] and Owen, Hershey and Gurdjian [10] expressed the belief that Trélat's [11] case of chondroma of the neck, reported in 1868, was probably one of chordoma and is, then, the earliest case of vertebral chordoma on record.

The history following the experimental work by Ribbert and Steiner [5] is composed largely of case reports and reviews of the subject. Articles by Stewart [12]; Coenen [13]; Stewart and Morin [14]; Machulko-Horbatzewitsch and Rochlin [15]; Owen, Hershey and Gurdjian [10]; Fletcher, Woltman and Adson [16]; Mabrey,[17] and Faust, Gilmore and Mudgett [18] offer complete reviews of the subject.

REVIEW OF CASES REPORTED IN THE LITERATURE

The recent review of Faust, Gilmore and Mudgett [18] shows that only 15.1 per cent of the chordomas are of the vertebral type. The

6. Potoschnig, G.: Ein Fall von malignem Chordom mit Metastasen, Beitr. z. path. Anat. u. z. allg. Path. **65**:356-362, 1919.

7. Klebs, E.: Ein Fall von Ecchondrosis spheno-occipitalis amylacea, Virchows Arch. f. path. Anat. **31**:396, 1864.

8. Raul, P., and Diss, A.: Chordome malin de la colonne vertébrale lombaire, Bull. et mém. Soc. anat. de Paris **94**:395-402, 1924.

9. DesJacques, R.: A propos d'un cas de chondrome de la colonne cervicale, Lyon chir. **24**:40-43, 1927.

10. Owen, C. I.; Hershey, L. N., and Gurdjian, E. S.: Chordoma Dorsalis of the Cervical Spine, Am. J. Cancer **16**:830-840, 1932.

11. Trélat, U.: Encondroma à marche rapide, Gaz. d. hôp. **41**:254, 1868.

12. Stewart, M. J.: Malignant Sacro-Coccygeal Chordoma, J. Path. & Bact. **25**:40-62, 1922.

13. Coenen, H.: Das Chordom, Beitr. z. klin. Chir. **133**:1-77, 1925.

14. Stewart, M. J., and Morin, J. E.: Chordoma: A Review with a Report of a New Sacro-Coccygeal Case, J. Path. & Bact. **29**:41-60, 1926.

15. Machulko-Horbatzewitsch, G. S., and Rochlin, L. L.: Pathomorphologie und Histogenese der Chordome, Arch. f. Psychiat. **89**:222-262, 1930.

16. Fletcher, E. M.; Woltman, H. W., and Adson, A. W.: Sacrococcygeal Chordomas, Arch. Neurol. & Psychiat. **33**:283-299 (Feb.) 1935.

17. Mabrey, R. E.: Chordoma: Study of One Hundred and Fifty Cases, Am. J. Cancer **25**:501-517, 1935.

18. Faust, D. B.; Gilmore, H. R., and Mudgett, C. S.: Chordomata: A Review of the Literature, with Report of a Sacrococcygeal Case, Ann. Int. Med. **21**:678-698, 1944.

classification devised by Coenen [13] and adapted by Gardner and Turner [19] has been modified slightly by us.

1. Cranial
   - (*a*) Sphenoid
   - (*b*) Spheno-occipital (clivis)
   - (*c*) Nasopharyngeal
   - (*d*) Dental (including maxillary and mandibular)
2. Vertebral
   - (*a*) Cervical (including chordomas arising from the odontoid process of the second cervical vertebra)
   - (*b*) Thoracic
   - (*c*) Lumbar
3. Sacrococcygeal (caudal)
   - (*a*) Antesacral
   - (*b*) Central
   - (*c*) Retrosacral

The case reported here is that of a vertebral chordoma, although finally the neoplasm largely replaced the entire sacrum.

Thirty-four cases of vertebral chordomas have been recorded. Davison and Weil [20] reported a malignant chordoma arising from the body of the third lumbar vertebra. In 1930 Machulko-Horbatzewitsch and Rochlin [15] reviewed 8 cases of vertebral chordoma. In his review of 150 cases in 1935, Mabrey [17] listed 14 cases of vertebral chordoma, the tumor being cervical in 7 cases, thoracic in 2 cases and lumbar in 5 cases. By 1944 Faust, Gilmore and Mudgett [18] had collected 20 cases occurring since 1935, bringing the total number of cases of vertebral chordoma to 34. They also reported a case of sacrococcygeal chordoma which had metastasized to the lungs and the adrenal gland. Since Faust, Gilmore and Mudgett's [18] survey of the literature, 12 cases of chordoma have beeen recorded, in only 2 of which is the tumor known to be vertebral. In the sacrococcygeal group widespread metastases occurred in over 50 per cent of the cases.[1]

Vertebral chordomas, except for the sacrococcygeal group, are largely found in the cervical region.[21] The lumbar chordomas rank second.[17] A case of chordoma occurring in the lumbar region of an osteomalacic mouse has been reported.[22]

REPORT OF CASE [23]

Mrs. I. G., a married woman aged 27, was admitted to the Montreal Neurological Institute on Aug. 31, 1943, complaining of pain in the lower part of the

19. Gardner, W. J., and Turner, O.: Cranial Chordomas: Clinical and Pathologic Study, Arch. Surg. **42**:411-425 (Feb.) 1941.

20. Davison, C., and Weil, A.: Malignant Chordoma of the Lumbar Region, Arch. Neurol. & Psychiat. **19**:415-423 (March) 1928.

21. Adson, A. W.; Kernohan, J. W., and Woltman, H. W.: Cranial and Cervical Chordomas, Arch. Neurol. & Psychiat. **33**:247-261 (Feb.) 1935.

22. Morpurgo, B., cited by Coenen.[13]

23. Dr. A. R. Elvidge permitted us to publish this case.

back of four months' duration and sciatic pain on the right side for three years. Occasional sciatic pain on the left side was noted for four months. She vaguely recalled having slipped on the floor, landing in a sitting position, five or six years previously, without noticeable injury or pain in the lower part of the back.

In 1940 she noted a sharp, recurring pain in the right calf, the posterior aspect of the left thigh and the left buttock, which persisted for many months. During the six months prior to admission she had observed that the right ankle seemed smaller than the left. Four months prior to her admission a persistent, sharp, ascending, stabbing pain was felt in both ankles, being more severe in the left one. There was a sensation of heat over the left leg, foot and thigh for about one-half hour every night, with occasional stiffness in the right foot and ankle. For about four months, intermittently, tiredness was felt in both legs, with gradual progressive weakness in both legs, particularly in the right. Codeine was taken to relieve pain, but sleep was poor. Coughing, sneezing, straining or bending forward or backward accentuated the pain in the leg and the lower part of the back.

At the time of onset of symptoms, in 1940, the patient had been treated for "inflammation of the sciatic nerve" and for "improper shoes." She was finally referred to the Montreal Neurological Institute, where a tentative diagnosis of ruptured intervertebral disk or tumor of the cord was made.

Examination revealed that the patient was well developed and well nourished. Pronounced scoliosis with convexity to the left and slight immobility of the lumbar portion of the spine were found. All movements of the spine accentuated the pain in the back and leg. There was tenderness over the fifth lumbar and first sacral transverse processes. The straight leg–raising test provoked neither pain in the back nor sciatic pain.

The patient was mentally alert, cooperative and well oriented, but nervous, rather timid and definitely anxious. The positive neurologic findings were diminution to pinprick over the distribution of the first to the fifth sacral nerves on the right side and a marked diminution in two point sensation over the whole right foot. There was considerable weakness in both legs. The tiptoe position was brief for both feet and was impossible to execute on one foot alone. Dorsiflexion of the foot was weak, especially on the right. There was slight atrophy of the right calf and the right anterior tibial muscle group, with moderate tenderness of the muscles of the right calf. The ankle jerk was absent bilaterally. Routine laboratory analyses gave normal results.

Roentgenographic examination on September 2 showed that the first sacral vertebra was not as completely united to the sacrum as usual, lying moderately higher in relation to the iliac crests and presenting a well formed separated laminal arch. The right sacroiliac joint was a little narrower than the left. The fifth lumbar–first sacral intervertebral disk was slightly narrowed.

A myelogram taken with iodized poppyseed oil showed arrest of the opaque column at the level of the superior border of the fifth lumbar vertebra, with some oil extending as far as the midportion of this vertebra, the level being slightly lower on the left.

Although the presence of a large herniated disk between the fifth lumbar and the first sacral vertebra could not be completely excluded, it was felt that the findings were much more in favor of a neoplasm which was filling the spinal canal.

On September 7 a right hemilaminectomy was performed by Dr. A. R. Elvidge, with subtotal removal of an extradural tumor. This epidural mass was observed lying at the level of the disk between the fifth lumbar and the first sacral vertebra

on the right side. It extended upward along the body of the fifth lumbar vertebra about half its length and into the sacral area for 2 to 3 cm. When the area was first exposed, a grayish, thick fluid was obtained; then grayish white portions of tissue were encountered. The mass was 4 cm. in length and 1 cm. in diameter. Microscopic examination showed that the tissue was a chordoma (fig. 1). A majority of the cells were embryonic, nonvacuolated, polygonal, epithelial types. All forms of transition were present, including the adult notochordal cell.

The postoperative course was uneventful. There was complete relief of sciatic pain; the wound healed satisfactorily, and on September 21 the patient was discharged and advised to return for roentgen therapy.

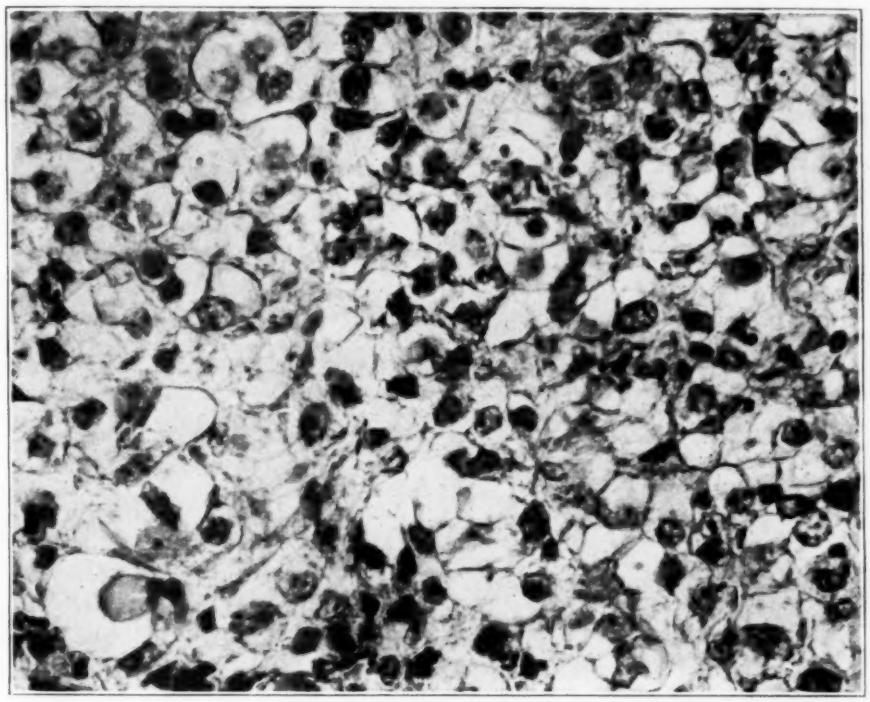

Fig. 1.—Appearance of the initial surgical specimen two years prior to death. Note the huge vacuolated cells with eccentric nuclei. Intracellular glycogen was present, and mitotic figures were not seen.

From Sept. 29 until Nov. 5, 1943 the patient received a full course of high voltage roentgen therapy over the lower lumbar and the sacral region. During this time she complained of mild pain in the lower part of the back. For six months she lived at home, with a fair degree of comfort. In April 1944 she again noted a gradual onset of sciatic pain on the left side, which later was replaced by burning pain. Urinary frequency, associated with anesthetic bowel and urinary movements, appeared, together with weakness in the left leg. She was readmitted to the hospital on June 10, 1944.

Examination revealed weakness of the muscles of the left anterior peroneal group and the calf; absence of the ankle jerk bilaterally; plantar extension on the right; immobility of the lower part of the back; slight scoliosis, with con-

vexity to the left; exquisite tenderness over the fifth lumbar and first sacral spinous processes; limitation of straight leg raising, which was more marked on the left, and analgesia over the area of the first to the fifth sacral vertebra bilaterally.

Roentgenographic examination on June 12, 1944 showed partial removal of the right lamina of the fifth lumbar vertebra. The anterior margin of the spinal canal opposite the first and second sacral vertebrae was farther forward than usual and was partially eroded. On June 23 Dr. Elvidge performed a laminectomy with removal of the recurrent chordoma at the level of the fourth and fifth lumbar and first sacral vertebrae bilaterally. The tissue removed consisted of a large piece of gray friable tissue, measuring 3 by 2 by 1 cm., and several smaller fragments, weighing 6 Gm. Microscopic examination again confirmed the diagnosis of chordoma. A few mitotic figures, not seen previously, were observed.

The patient's condition was improved at the time of her discharge, four months after operation. She no longer complained of sciatica, and the motor power in both legs was fairly good. She was able to walk without help. Roentgenographic examination on Oct. 10, 1944 showed no change.

For four months she suffered occasional sharp, shocklike pains in the buttocks and the posterior aspect of both thighs down to the ankles. The pain became so accentuated that in January 1945 she went to bed permanently. Urinary and rectal stress incontinence had persisted from the time she had last left the hospital.

On Feb. 12, 1945, the patient became completely paralyzed in both legs, with total cessation of pain in both lower limbs. On the following day she was readmitted to the Montreal Neurological Institute, where examination revealed complete paraplegia. There were hyperesthesia and hypalgesia from the twelfth thoracic dermatome down, with loss of sensation over the tenth and eleventh thoracic segments. Roentgenographic examination showed increasing destruction of bone in the sacral region and a lesion involving the body of the eleventh thoracic vertebra.

Dr. Elvidge performed a third laminectomy and removed 15 Gm. of extradural reddish, granular tumor tissue lying over the tenth thoracic vertebra and extending deep into the body of the eleventh thoracic vertebra.

Microscopic examination revealed cells similar to those in the chordoma tissue removed previously. In addition, it was noted that the neoplasm was invading bone to a pronounced extent.

The postoperative course was progressively downhill. Neither motor nor sensory power in the lower limbs was ever regained. A swelling in the left temporal region of the skull developed and was followed by papilledema. Roentgenographic examination of the skull and sinuses on March 28, 1945 showed extensive destruction of a considerable portion of the left side of the skull. This had noticeably increased by April 16. She died six months later.

NECROPSY

General Examination.—Autopsy was performed seventeen hours post mortem. The body was extremely emaciated, and pronounced edema of both feet was noted. Decubitus ulcers were present over both heels, on the right buttock and in the right subscapular region.

A small amount of fluid was present in the pleural cavity amounting to 100 cc. on the right side and 50 cc. on the left side. The portion of the pleural cavity not containing fluid was obliterated by fibrous adhesions. The visceral pleura

bulged on each side, owing to the presence of tumor nodules. In the upper part of the inferior lobe of the left lung and in a corresponding position within the right lung was located a small tumor nodule. In the peripancreatic soft tissues a rather firm, small nodule was identified. The axillary and iliac lymph nodes were almost completely replaced by neoplasm. Examination of other abdominal and thoracic structures showed only signs of severe emaciation.

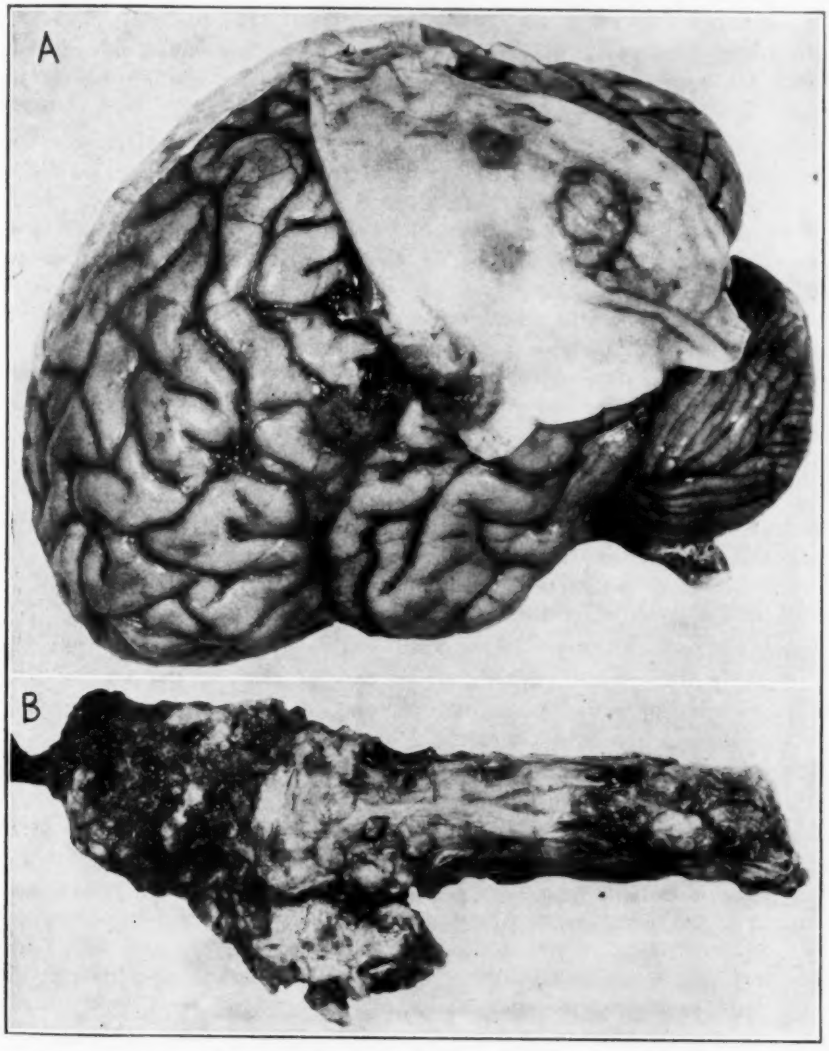

Fig. 2.—*A*, the brain after removal. Note the presence of large dural nodules, one of which is shown invading the brain just above the sylvian fissure. The photomicrographs shown in figures 5 *A* and *B* and 7 are taken from the nodule invading the brain. *B*, gross appearance of the lumbar and sacral regions prior to dissection. Note the massive replacement of the sacrum by the tumor mass. For photomicrographs of sections see figures 5 and 6.

Neurologic Study.—Extensive destruction involved a considerable portion of the left side of the skull. The destruction was most marked in the region of

the coronal suture of the frontal bone. It extended backward into the posterior part of the parietal bone and forward to involve the superior orbital plate.

Over the frontal and temporal regions on the left side the dura was eroded by several nodules projecting from the outer surface of the dura. The reflected dura showed two nodules in the anterior frontal area (fig. 2*A*). The arachnoid was thickened. A large, irregular mass, measuring 6 by 4 cm., was attached firmly to the underlying brain. The arachnoid was destroyed at this point, and the brain was invaded by the mass.

Horizontal sections of the brain at 2 cm. intervals revealed no additional lesions. The upper cervical and the thoracic region of the spinal cord appeared normal.

Vertebral Bodies and Sacrum.—The lower part of the vertebral column, from the twelfth thoracic vertebra to the coccyx, was removed (fig. 2*B*). The body of the twelfth thoracic vertebra was soft, bloated and soggy, and many soft nodules could be palpated. The bodies of the lumbar vertebrae from the first to the fourth appeared normal. Caudal to the fourth lumbar vertebra the spine was mostly replaced by a large, irregular mass of tumor; yet the shape and appearance of the fifth lumbar vertebra, the sacrum and the coccyx could still be seen. This mass was filled with multiple nodules, which were 0.5 to 3 cm. in diameter. Each nodule was irregular in shape and rubbery in consistency and showed necrotic areas easily detached from the mass. Firm islands of bone were also identified within the tumor.

Transverse Processes and Intervertebral Joints.—The superior articular facets of the sacrum were the only bony structures of the sacrum retaining a normal appearance. The capsules of the joints were destroyed, and there was evidence of marginal softening and darkening of the articular surfaces. There was complete destruction of the joints between the twelfth thoracic and the first lumbar vertebrae. The other intervertebral joints were normal.

Two small nodules of tumor were noted on the left anterolateral aspect of the body of the fourth lumbar vertebra, which were adherent to the anterior longitudinal ligament and to the muscle tendons inserting on the vertebral body at this level. Another such nodule, measuring 2 by 1.5 cm., was observed opposite the left anterolateral aspect of the body of the first lumbar vertebra. It was firmly adherent to the adjacent structures.

Dissection.—A horizontal section was made through the inferior border of the disk between the second and the third lumbar vertebrae, the plane of the cut being slightly inferior and posterior. A midsagittal section through the bodies of the third, fourth and fifth lumbar vertebrae and the sacral tumor mass was prepared. Bilateral laminectomy of the twelfth thoracic and the first and second lumbar vertebrae, a horizontal section parallel to the inferior aspect of the disk between the eleventh and the twelfth thoracic vertebrae and a midsagittal section through the bodies of the twelfth thoracic and the first and second lumbar vertebrae were made.

The section through the disk between the second and the third lumbar vertebrae showed that the annulus fibrosus, the nucleus pulposus and the cartilage plate of the superior aspect of the third lumbar vertebra were intact. The normal appearance of the intervertebral space seemed to rule out metastases by direct extension, suggesting that the disk had acted as a barrier to the spread of the tumor. On removal of the superior cartilage plate, the cancellous bone of the third lumbar vertebra seemed normal. The dura was thickened and

adherent to the intervertebral canal. The meninges and the nerve roots of the cauda equina appeared normal up to the level of this section. In the section below, however, the nerve roots and the pia-arachnoid were fused into one soft, gelatinous mass, in which nerve roots could not be identified. This tumor mass was adherent to the dura.

The midsagittal section through the bodies of the third, fourth and fifth sacral vertebrae and the sacrum showed dissemination of the tumor to all structures. The greatest amount of destruction was in the sacrum and the least in the intervertebral disks.

The sacrum was composed of debris of cancellous bone, tumor and necrotic tissue, forming a firm, ragged, rubbery mass. The largest single tumor nodule lay in the posterior halves of the bodies of the first and second sacral vertebrae. The sacral disks were recognized, their central portions being almost normal in appearance. There was beginning destruction of the anterior and posterior edges. The sacral canal could not be identified.

The body of the fifth lumbar vertebra was almost completely replaced by tumor and necrotic tissue. Fragments of cancellous bone still persisted in the right half of the body of this vertebra.

The body of the fourth lumbar vertebra was grossly normal. There was a dark brown area of liquefaction in its posterior half.

The only pathologic change in the body of the third lumbar vertebra was the presence of a small crypt, 1 cm. in depth, at the level of the upper third of the posterior aspect, establishing a communication between the vertebral canal and the cancellous bone. This crypt contained the same thick, brown, gelatinous substance which was present in the cancellous bone of the fourth lumbar vertebra. The disks between the third and the fourth lumbar and the fourth and the fifth lumbar vertebrae and their limiting cartilage plates were intact.

The bony structure of the spinal canal showed no gross abnormalities anteriorly and laterally, at the levels of the third and fourth lumbar vertebrae. The posterior aspect was softened and partially replaced by tumor. From the fourth lumbar vertebra caudally the spinal canal was destroyed and replaced by tumor. The dura was densely adherent to the canal. The nerve roots could no longer be distinguished. They had fused into a soft, jelly-like mass of tumor and necrotic tissue, which was friable and of a dull gray color and showed scattered flecks of yellow tissue throughout.

On the inner aspect of the removed laminas of the twelfth thoracic and the first and second lumbar vertebrae, there existed small masses of a yellowish, gelatinous substance, resembling fat which had undergone degeneration. This substance was found to dissolve in ether. The nerve roots were normal in appearance. The perineural fat usually observed at the entrance to the foramens was replaced by the same yellowish, gelatinous substance adherent to the ligamentum flavum. A posterior longitudinal incision was made in the dura. There was pronounced vascular congestion of the posterior vessels lying on the nerve roots. The arachnoid was of normal appearance. On dissection, it was noted that the nerve roots could be separated and identified at the level of the second lumbar vertebra. Cephalad to this level they were fused. A few nerves could be lifted away from the bundle peripherally.

The horizontal section parallel to the inferior aspect of the disk between the twelfth thoracic and the first lumbar vertebrae revealed complete destruction of the body of the twelfth thoracic vertebra of the intervertebral canal and its contents, of the disk and its cartilage plates and of the superior aspect of the

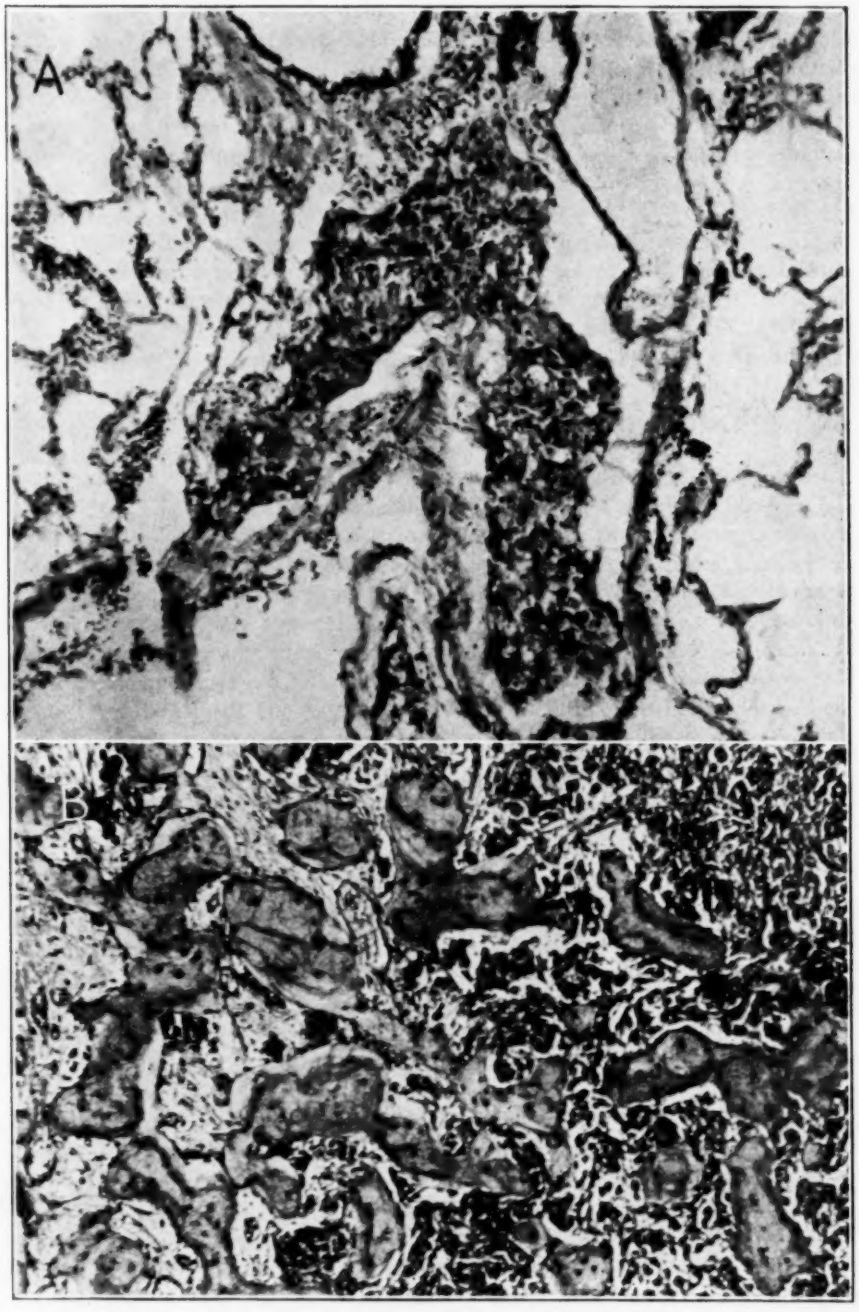

Fig. 3.—*A*, photomicrograph showing tumor nodule in a large vein of the lung near the pleura. *B*, neoplasm invading the bone of the skull overlying the dural nodule shown in figure 2 *A*. Hematoxylin and eosin stain.

annulus fibrosus of the disk. A small portion of the annulus of the disk between the twelfth thoracic and the first lumbar vertebrae could be identified.

The midsagittal section through the twelfth thoracic and the first and second lumbar vertebrae showed destruction of the body of the twelfth thoracic vertebra by tumor tissue. The first lumbar vertebra seemed grossly normal in appearance, and the disk between the first and second lumbar vertebrae was intact. The body of the second lumbar vertebra revealed the presence of a large, whitish, calcified nodule, directly above the nucleus pulposus of the disk between the second and the third lumbar vertebrae and distinctly separated from the disk by an intact cartilage plate. A second nodule filled the cancellous bone anteriorly. The central portion of this

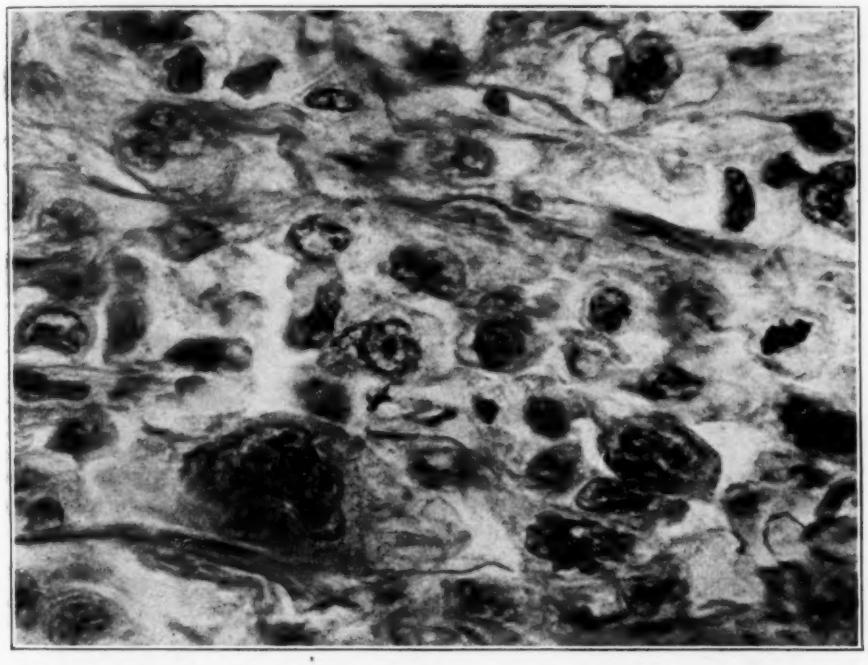

Fig. 4.—Marked pleomorphism of cell types in the axillary lymph node. Note the large multinucleated tumor giant cell and the presence of a mitotic figure.

vertebra was replaced by a brown, syrupy substance. The dura was firmly adherent by numerous fine, glossy, distensible membranous bands to the inner surface of the spinal canal.

HISTOLOGIC REPORT

The section taken through the nodule in the lung revealed mixed atelectasis and emphysema, with some thickening of the pleurae (fig. 3 *A*). Patchy hyperemia of the parenchyma was apparent. Tumor cells were seen within the lymphatics and the blood vessels. The tumor nodule seen grossly was subpleural and necrotic. The tumor cells formed ill defined syncytial sheets and masses. Vacuolated spaces of small size were seen among the tumor cells. The cytoplasm stained deeply with both eosin and hematoxylin. The nuclei were abundant and large, with little chromatin. Prominent nucleoli were common, and pleomorphism was conspicuous.

Sections of the axillary and iliac lymph nodes (fig. 4) revealed that the neoplasm had largely replaced the normal architecture. The tumor cells resembled those

seen in the lungs except that there was a much greater tendency for the cell to preserve its identity as a discrete polygonal entity. In the axillary node, nuclear and cytoplasmic vacuolation was prominent, and necrosis was present. There was an abundance of intercellular and intracellular glycogen, demonstrated by the

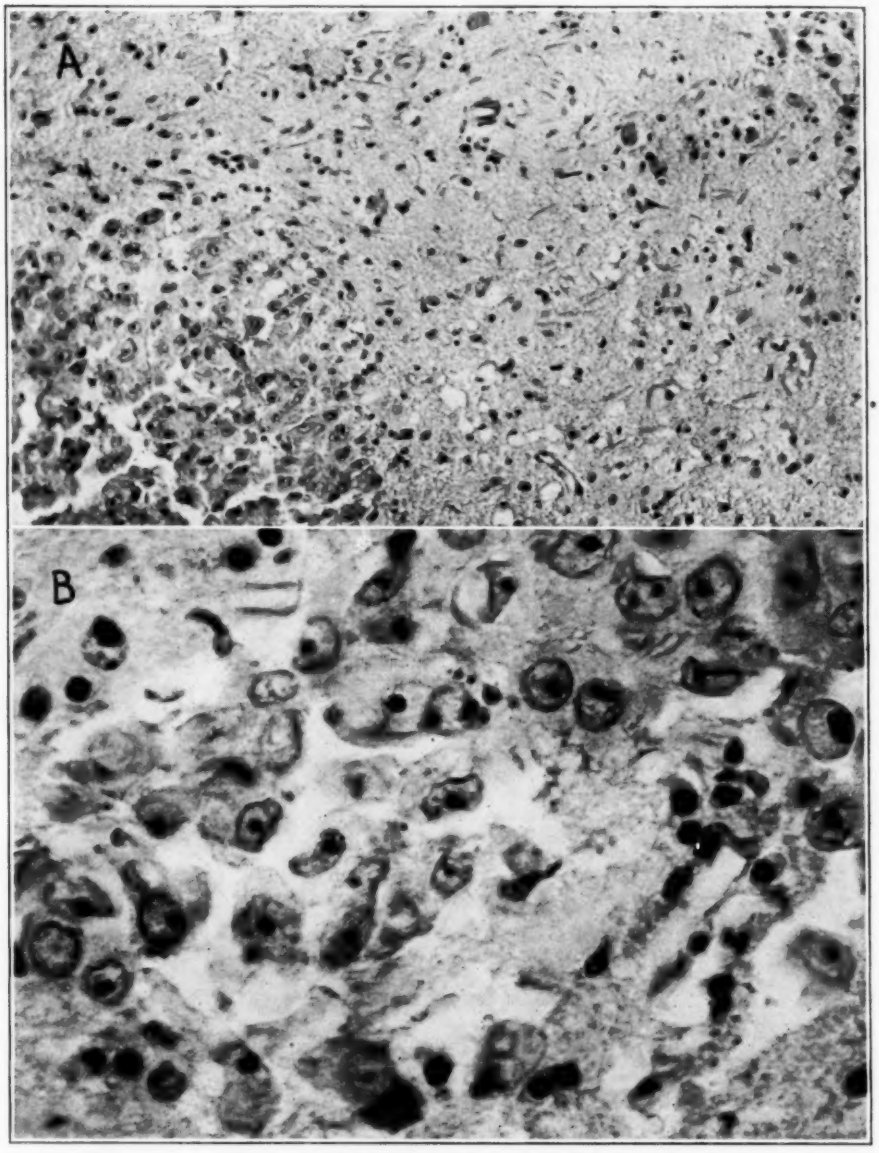

Fig. 5.—Low (*A*) and high (*B*) power views of the tumor invading the left parietal region (fig. 2 *A*). Note the direct invasion, lack of encapsulation of the tumor, presence of scattered neoplastic cells far ahead of the primary mass, large number of plump astrocytes, large cells with prominent nuclei and of varying shapes, hyperchromatic nucleoli and occasional vacuolation of the cytoplasm. Hematoxylin–Van Gieson stain. Compare with figure 7.

Best carmine stain in specimens fixed in alcohol. Vacuolation of cells in the iliac nodes was prominent. The cells tended to be discrete, dark staining and not so large as those of the lung and axillary nodes. They were pleomorphic. Neoplastic cells were noted within the lymphatics and the blood vessels of all the lymph nodes.

A section taken through the skull (fig. 3 *B*) revealed predominating destruction of bone by invading tumor. Formation of new bone and proliferation of fibrous tissue were also seen. The cell type showed less pleomorphism and less vacuolation than the cells seen in the metastases in the lungs. Giant cells were observed. Mitotic figures were not seen.

In the peripancreatic tissue a lymph node was almost entirely replaced by tumor. The cell type showed minimal pleomorphism. The cytoplasm stained dark red with eosin. The nucleus was large and round. Chromatin was small in amount and was composed of alternating small and large granular globules. Intracytoplasmic and intranuclear vacuolation was observed but was rather uncommon. Mitoses were frequent.

Routine histologic examination of all other viscera failed to show the presence of metastases.

A section taken through one of the dural nodules demonstrated the neoplastic invasion of the dura. The internal layer was well preserved. The middle and outer layers were replaced by tumor and newly formed fibrous tissue. Projecting from this layer of fibrous and neoplastic tissue was an external nodule of tumor, which was divided into lobules by fibrous tissue. The cell type was pleomorphic and was made up of large polygonal cells. The nucleus presented an irregular outline and little chromatin. A central nucleolus was commonly noted. Intracytoplasmic and intranuclear vacuolation was not uncommon. The intracytoplasmic vacuolation was so great within some of the cells as not only to distend the cell but to give the impression that the nucleus was being expressed from the cytoplasm. Mitoses were not seen.

A section taken from the left frontoparietal region, at the lower end of the rolandic fissure (fig. 5), showed a small tumor nodule invading and destroying the cortex and the underlying white matter. A few smaller nodules were identified within the plexiform layer. The cells were large and closely packed. The pleomorphism was not so prominent as that seen in the lungs and in the lymph nodes. However, intracytoplasmic vacuolations were more numerous. Mitoses were not seen. Small areas of demyelination and small cysts were observed in the white matter. Perivascular infiltration of mononuclear cells was noted deep within the brain. There was surprisingly little glial reaction to the invading neoplasm.

The lesion taken from the extradural space at the level of the fourth lumbar vertebra was rather fibrous. A large sheet of fibrous tissue gave rise to trabeculae, which formed a support for the tumor cells. There were small, suggestive, alveolar-like aggregates of cells; yet in some areas reticulum separated a large number of individual cells. Massive necrosis with huge deposits of fat was observed.

A section taken to demonstrate the relation of the tumor to the lumbar plexus revealed only fragments of nerve fibers enclosed in a large mass of densely fibrous tissue with islands of tumor cells interspersed. The blood vessels of largest caliber were filled with tumor and necrotic debris. Many of the vessels were thrombosed. The most pronounced pleomorphism existed here. Numerous giant cells were seen. Mitoses were common. Many degenerating nuclear forms were observed, and amitotic division was present.

A cross section of the spinal cord at the level of the twelfth thoracic segment showed a greatly thickened dura with a large mass of tumor attached. Arising from the outer layer of the dura were large sheets of fibrous tissue, which divided a necrotic mass into smaller lobules. The same cellular characteristics existed

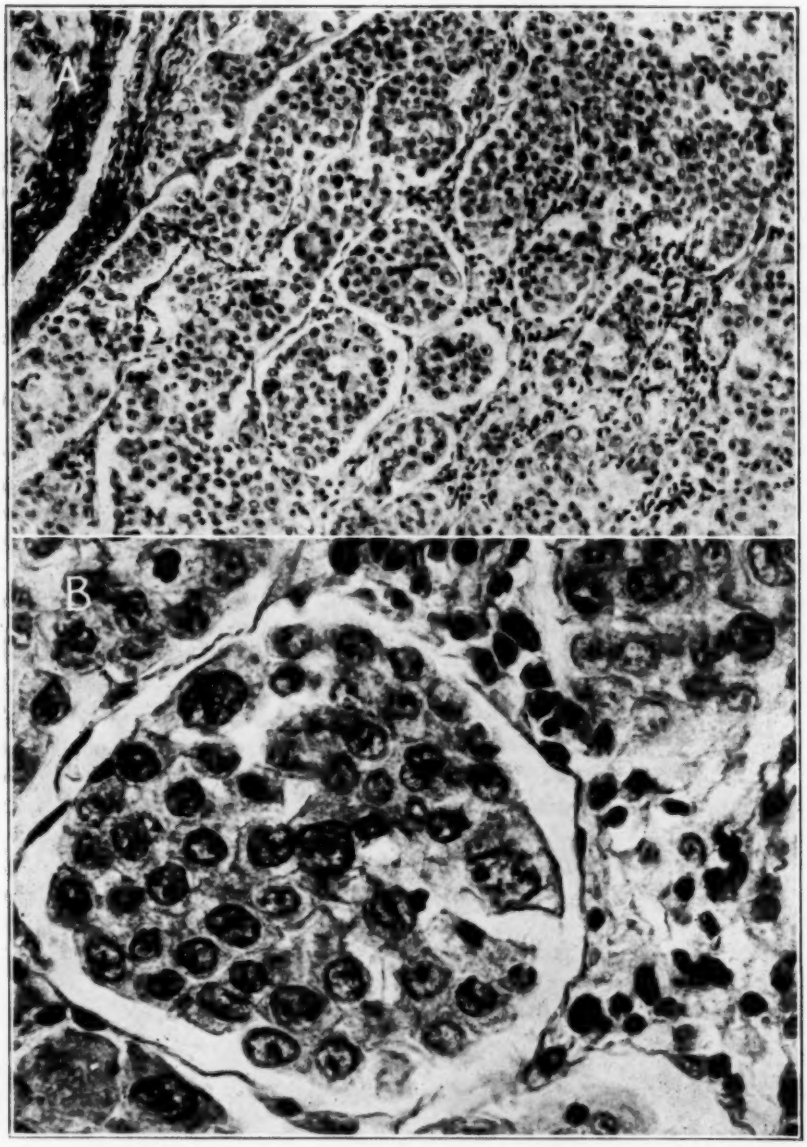

Fig. 6.—Appearance of the neoplastic nodule lying opposite the left anterolateral aspect of the body of the first lumbar vertebra. High (*A*) and low (*B*) power views, showing the lobular arrangement of the cells within well encapsulated masses of tumor. Note the resemblance to alveolar carcinoma.

here as were seen in the extradural mass which lay opposite the fourth lumbar vertebra. The spinal cord revealed massive destruction, presumably due to extradural pressure.

A section taken from the anterior half of the body of the fourth lumbar vertebra, including the intervertebral disk, the cartilage plate, the annulus fibrosus and the cancellous bone, showed no invasion of the intervertebral disk or of the cartilage plate by tumor tissue. Neoplastic tissue was seen replacing the marrow of the cancellous bone and destroying the bony trabeculae. A section of the tumor nodule on the left anterolateral aspect of the body of the first lumbar vertebra (fig. 6 *A* and *B*) showed the lobular arrangement of cells within well encapsulated masses of tumor resembling alveolar carcinoma.

Dr. Cone [24] described a case similar histologically in 1929, emphasizing the presence of intracytoplasmic and intranuclear inclusion bodies. He related the cell type to the cells seen in the notochord of the chick embryo at a stage at which the notochord is disappearing. We were unable to demonstrate these inclusions in our material.

COMMENT

The initial complaints of the patient whose case is reported here were identical with the symptoms and signs of a protruded intervertebral disk at the fifth lumbar–first sacral interspace. For three years sciatica on the right side was present intermittently, following a fall two years previously. The roentgenologic examination proved interesting in showing that the first sacral vertebra was not so completely united to the sacrum as usual, lying moderately higher in relation to the iliac crests and presenting a well formed, separated laminal arch. The diagnosis of tumor of the cord was based on myelographic evidence, and the diagnosis of the tumor type was made from the surgical specimen. At operation, an extradural mass was observed opposite the disk between the fifth lumbar and the first sacral vertebra, which could be followed into the body of the fifth lumbar vertebra.

Three surgical removals were carried out in the lumbar region within a period of one and one-half years. The first operation was followed by a course of roentgen therapy. Between operations the patient was comfortable.

The unusual pathologic features of the case are the metastases to the brain, lungs, pancreas, sacrum and axillary and iliac lymph nodes. The rectum was free of neoplastic involvement. Metastases to the brain have not previously been recorded. Extensive pulmonary metastases have been reported without involvement of the brain.[18]

Alezais and Peyron [25] presented the histologic criteria for chordoma. They stated that vacuolation of the cellular element, affecting the cytoplasm and the intercellular spaces about the ectoplasm, was a specific characteristic of chordal tissue. Vacuoles were thought to contain a

24. Personal communication to the authors.

25. Alezais, H., and Peyron, A.: Sur l'histiogenèse et l'origine des chordomes, Compt. rend. Acad. d. sc. **174**:419-421, 1922.

mucin-like substance. The cellular arrangement was described as that of groups of cells, about cavities, and appearing prismatic or cuboidal. There may be plain strips of cells of epithelial type, with dense cytoplasm filled with vacuoles, interspaced regularly with vascular endothelium. Cellular elements similar to those seen in sarcomas (fusiform or polymorphous in type) may be present. A fine network of fibrils appearing in vacuolated zones tends to make the cellular limits disappear. Alezais and Peyron [25] also stated the belief that the various appearances of chordoma lesions correspond to the classic stages of the evolution of the primitive notochord—first a hollow tube, then a solid cord of undifferentiated epithelial cells and, finally, the vacuolation, formation of mucin and fibrillation, which indicate its adaptation to a supporting role. Fletcher, Woltman and Adson [16] expressed the belief that notochordal tumors, although they may resemble either epithelial or mesodermal neoplasms, have specific characteristics. Importance was attached to the formation of intracellular and extracellular mucus; the presence of physaliferous or huge vacuolated, mucus-containing cells; the lobular arrangement of the tumor cells, which usually grow in cords; the occasional occurrence of vacuolation of the nuclei, and the close resemblance to notochordal tissue, as seen in the nucleus pulposus of the intervertebral disks.

The formation of mucus is the most primitive function of notochordal tissue. Thus, its presence in notochordal neoplasms would seem to be of prime importance in making the histologic diagnosis. In the most malignant types of chordoma the production of mucus is the last of the characteristics to disappear as the number of undifferentiated cells increase. The lesions described in the present case showed the presence of both intracellular and extracellular mucus, demonstrated by Best's carmine stain for glycogen on alcohol-fixed tissue. These lesions also show the histologic criteria of advancing malignancy: numerous mitotic figures, cellular pleomorphism, hyperchromatic and irregular nuclei and multinucleated tumor giant cells. Numerous vacuolated nuclei were present in all lesions. Intracytoplasmic and intranuclear inclusion bodies were not demonstrated. The close resemblance to notochordal tissue is suggested by the appearance of the original surgical specimen. Stewart and Morin [14] asserted that the diagnosis of chordoma can be made with certainty only when the characteristic vacuolation and production of mucin are present in at least a portion of the growth.

Whether or not chordomas form cartilage is an interesting point. Faust, Gilmore and Mudgett [18] suggested that areas showing almost acellular fibrillar material, with scattered vacuolated chordoma cells, give the appearance of cartilage. Gardner and Turner [19] included a photomicrograph of tissue which has the appearance of cartilage and which is composed of "vacuolated cells within a homogeneous matrix."

Intranuclear, intracytoplasmic and intercellular glycogen was demonstrated in the original surgical specimen and in the metastatic lesions studied post mortem (fig. 7). The presence of intracellular glycogen has been held responsible for the cytoplasmic vacuolation in every case.[26] Nuclear vacuolation has been commented on, but the cause is still undetermined.[27] In cases of a highly malignant growth mitoses are common. The odd-shaped nuclear forms, stated by Raul and Diss [8] to indicate proliferation of cells by amitosis, are not considered evidence of cell multiplication.

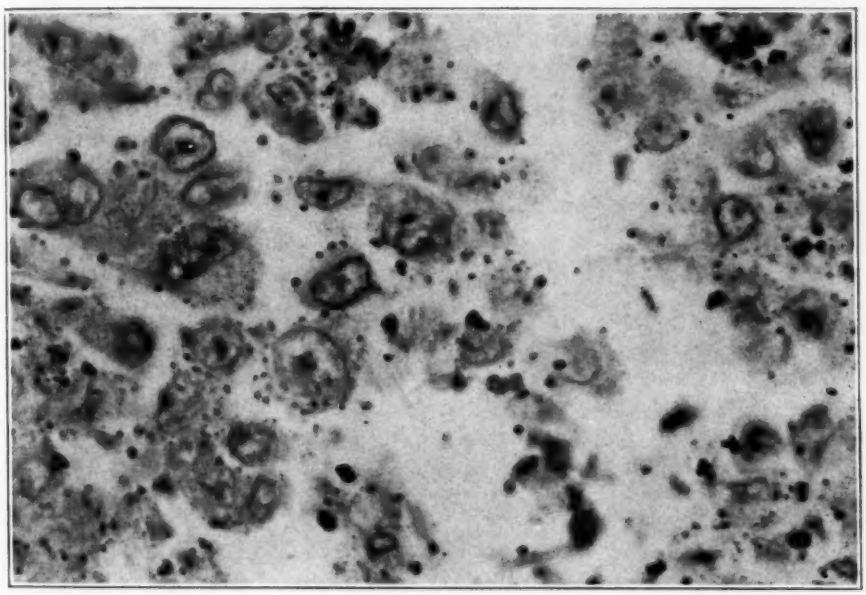

Fig. 7.—Presence of glycogen in the cerebral metastatic lesion. Best's carmine stain for glycogen on alcohol-fixed pyroxylin sections.

SUMMARY

In many of the 34 previously reported cases of vertebral chordoma metastases to various structures have occurred. The case here reported, with metastases to the brain, is believed to be unique, and the neoplasm is classified as vertebral chordoma on the basis of operative studies. Postmortem examination, two and one-half years later, showed metastases to the sacrum, pancreas, lungs, brain and axillary and iliac lymph nodes.

26. Mathias: Ein Beitrag zur Lehre vom malignem Chordom, Verhandl. d. deutsch. path. Gesellsch., 1923, p. 198.

27. Alexander, W. A., and Struthers, J. W.: Sacrococcygeal Chordoma, J Path. & Bact. **29**:61-64, 1926. Stewart.[12]

Histologic examination of the lesions revealed the presence of vacuolation of the cellular element, affecting the cytoplasm, nucleus and intercellular spaces about the ectoplasm. The vacuoles were shown to contain a small amount of a mucin-like substance. Cells were arranged about cavities and in lobular forms. Plain strips of cells of epithelial type, with dense cytoplasm filled with vacuoles, interspaced regularly with vascular endothelium, were not uncommon. A fine network of fibrils, appearing in vacuolated zones, could be demonstrated in the local invasive mass of neoplasm. Both mesodermal and epithelial-like sections were identified, the local mass being related more specifically to the epithelial type, while the metastatic lesions resembled the mesodermal type. The close resemblance to notochordal tissue, as seen in the nucleus pulposus of the intevertebral disks, was shown only in the original surgical specimen.

Formation of mucus is considered the most primitive function of notochordal tissue, and the presence of mucus in a portion of the lesions is necessary in arriving at a proper diagnosis of chordoma. Chordomas may form cartilage, or at least cartilage-like structures. That glycogen can be held responsible for vacuolation in every case still remains unproved.

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HISTOPATHOLOGIC CHANGES ASSOCIATED WITH HUMAN POLIOMYELITIS

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CINCINNATI

IN SPITE of numerous studies concerning the histopathology of human poliomyelitis, the following problems remain controversial: (1) the localization of the disease and its distribution; (2) the primary type of the essential lesions (whether the alterations in the nerve cells or the inflammatory mesodermal reactions comprise the primary process); (3) the correlation of the neuronal damage and the mesodermal-glial alterations, and (4) the role played by the microglia.

The purpose of this paper is to review some of the conflicting views and to attempt to arrive at an acceptable conclusion concerning some of the aforementioned problems. This presentation is the result of a detailed study of 6 cases of acute anterior poliomyelitis.

Until recently the attention of clinicians and pathologists interested in poliomyelitis was centered almost exclusively on the spinal cord and the medulla. Since 1929, however, when Thomas and Lhermitte [3] pointed out that the motor cortex may be affected, increasing attention has been paid to the rest of the central nervous system. A detailed description of all regions of the central nervous system consistently revealing tissue alterations will be given.

HISTOPATHOLOGIC STUDY

The histopathologic lesions were of two principal types: (1) ectodermal changes and (2) mesodermal reactions. The ectodermal alterations were degenerative and the mesodermal proliferative. The former related to susceptible nerve cells; the latter, to microglial elements.

Spinal Cord.—Ectodermal (Degenerative) Changes: Degeneration of nerve cells was at its maximum at the cervical and lumbar levels of the spinal cord, where commonly the large majority of the anterior horn

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Read at the Seventy-First Annual Meeting of the American Neurological Association, San Francisco, June 26, 1946.

From the Laboratory of Neuropathology, Cincinnati General Hospital, and the University of Cincinnati College of Medicine.

1 and 2. Footnotes deleted by the author.

3. Thomas, A., and Lhermitte, J.: Les lésions cérébrales et médullaires de la poliomyélitie aiguë de l'adulte, Rev. neurol. **36**:1242, 1929.

cells were completely destroyed and replaced by a tremendous number of proliferated microglia cells (fig. 1). In the dorsal or the high cervical region in some cases, however, the neuronal destruction was less severe. A considerable number of anterior horn cells were spared from complete destruction; they revealed the following characteristic sequence of degeneration: Central chromatolysis or complete dissolution of the Nissl granules was frequently associated with considerable swelling of both nucleus

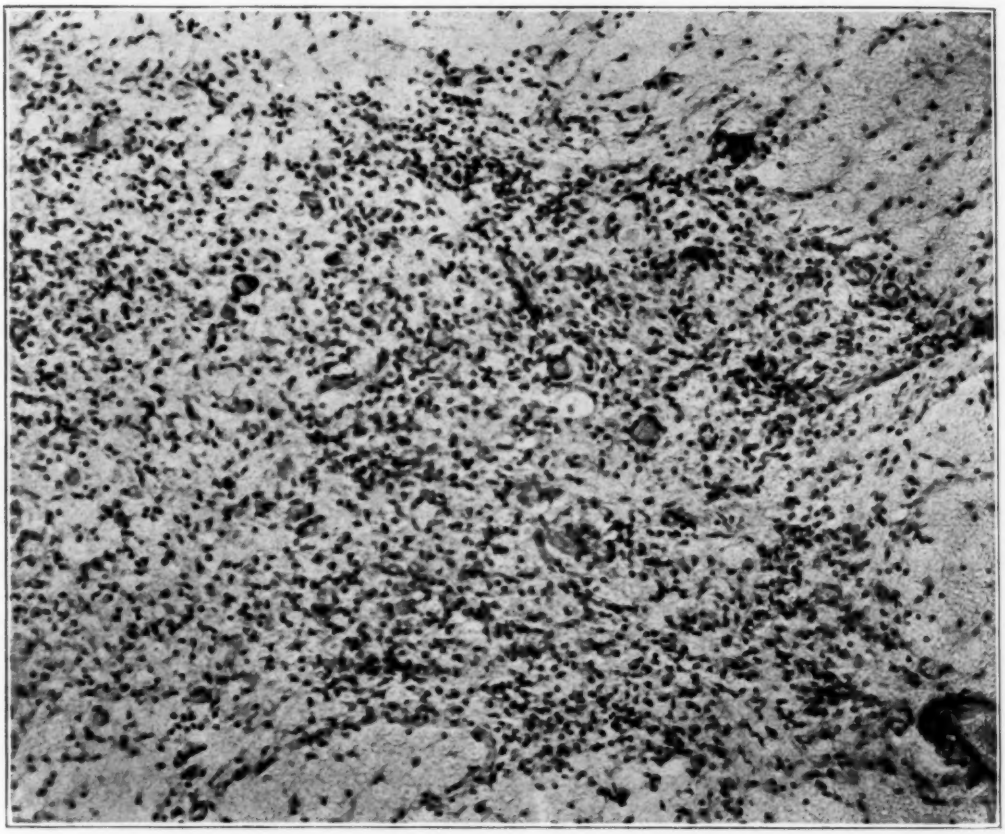

Fig. 1.—Anterior horn of the cervical portion of the spinal cord. Almost all the nerve cells are destroyed and replaced by a tremendous number of proliferated microglial cells. Cresyl violet stain; × 160.

and cytoplasm, with loss of stainability. Occasionally, however, the nucleus was shrunken, stained darker than usual and occupied an eccentric position in the cell. The cytoplasm had a reticulated appearance and was irregularly outlined, eaten away and invaded by various phagocytes (neuronophagia). In some instances the nerve cells were merely surrounded, but not invaded, by glia cells (satellitosis). In preparations stained with the Bodian silver impregnation method, the intracellular

network appeared distorted, and the neurofibrils were irregularly stained; some of them were heavily impregnated with silver and appeared considerably thicker than normal. In some cells there was granular disintegration or complete loss of the neurofibrils. Neuronal destruction was not always confined to the anterior horn cells; frequently the cells of the posterior horn were damaged, though less severely than those of

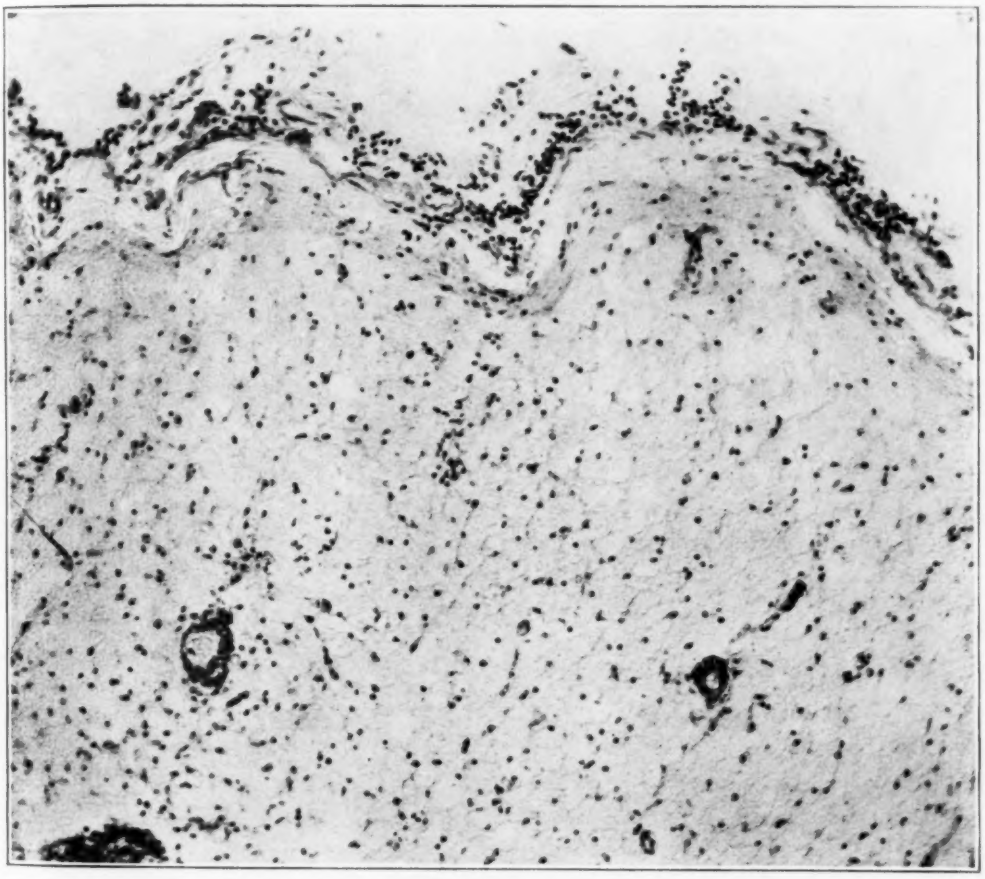

Fig. 2.—Infiltration of the spinal leptomeninges with lymphocytes, fibroblasts and endothelial cells. Cresyl violet stain; × 180.

the anterior horn. The cells of Clarke's column were mostly spared from degeneration.

Mesodermal (Proliferative) Alterations: Concomitant with neuronal destruction, there was a striking proliferation of the microglia. With low magnification the whole gray matter appeared very cellular (fig. 1). The bulk of the cells were involved in very severe neuronal destruction, as in the central portions of the anterior horns; there was a slight degree of perivascular cuffing. The infiltrating cells were predominantly small

lymphocytes, with a variable proportion of adventitial and endothelial elements. These cells were usually confined to the adventitial space of Virchow and Robin. Seldom did the infiltrative cells cross the pial-glial membrane to invade the surrounding nerve tissue. The density of perivascular accumulations of cells was variable; they were either composed of a few lymphocytes or formed a broad cuff, many cells deep.

The inflammatory changes described in the spinal cord were also present in the leptomeninges. Cellular exudates encircled some of the pial vessels (fig. 2). The pia of the anterior median fissure and the

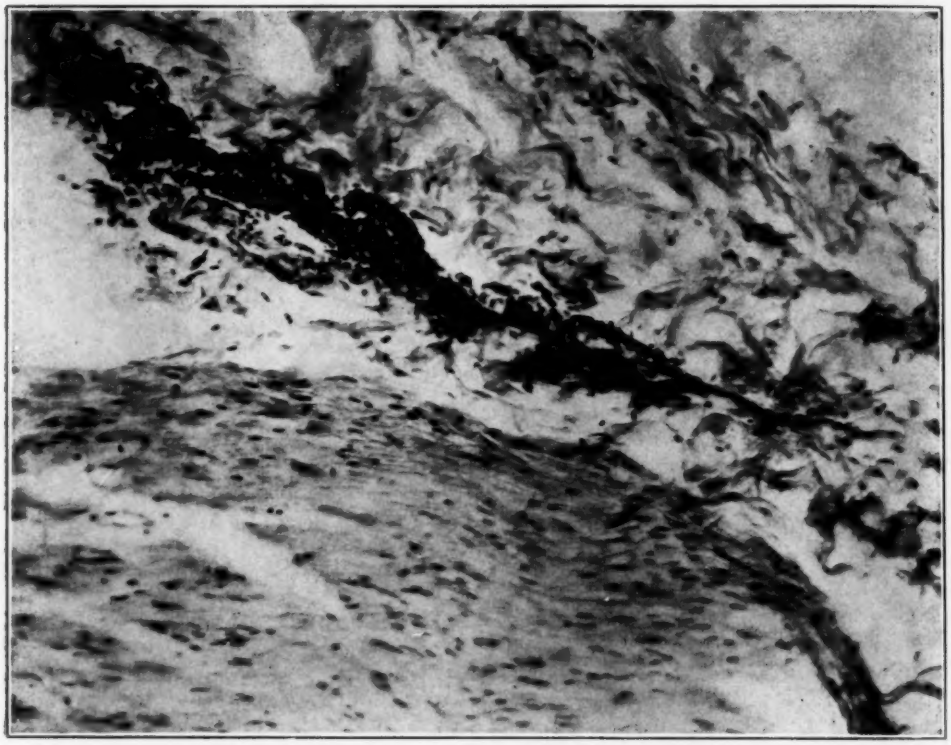

Fig. 3.—Dense accumulation of lymphocytes about the anterior roots of the spinal cord. Hematoxylin and eosin stain; × 180.

zones of entrance of the dorsal nerve roots were the favorite locations for the infiltrates, the composition of which was the same as that of the infiltrates in the spinal cord. Lymphocytes, fibroblasts and endothelial cells were present, in varying quantities. Plasma cells were not seen. It is worth emphasizing that the degree of meningeal infiltration varied considerably at different levels of the spinal cord. The cerebral meninges were affected only in the region of the midbrain and the cerebellum.

Paralleling the destruction of nerve cells and reactive glial changes, a far advanced degeneration of the anterior nerve roots was disclosed.

There was destruction of myelin sheaths, which appeared to be broken up into small fragments. Degeneration of the axons was likewise seen in some of the anterior nerve roots, as well as in the white fibers of the anterior horns. In some cases the anterior nerve roots showed scattered areas of focal infiltration with lymphocytes (fig. 3). The mesodermal as well as the ectodermal, alterations were most pronounced in the cervical and lumbar enlargements, but no level escaped severe damage.

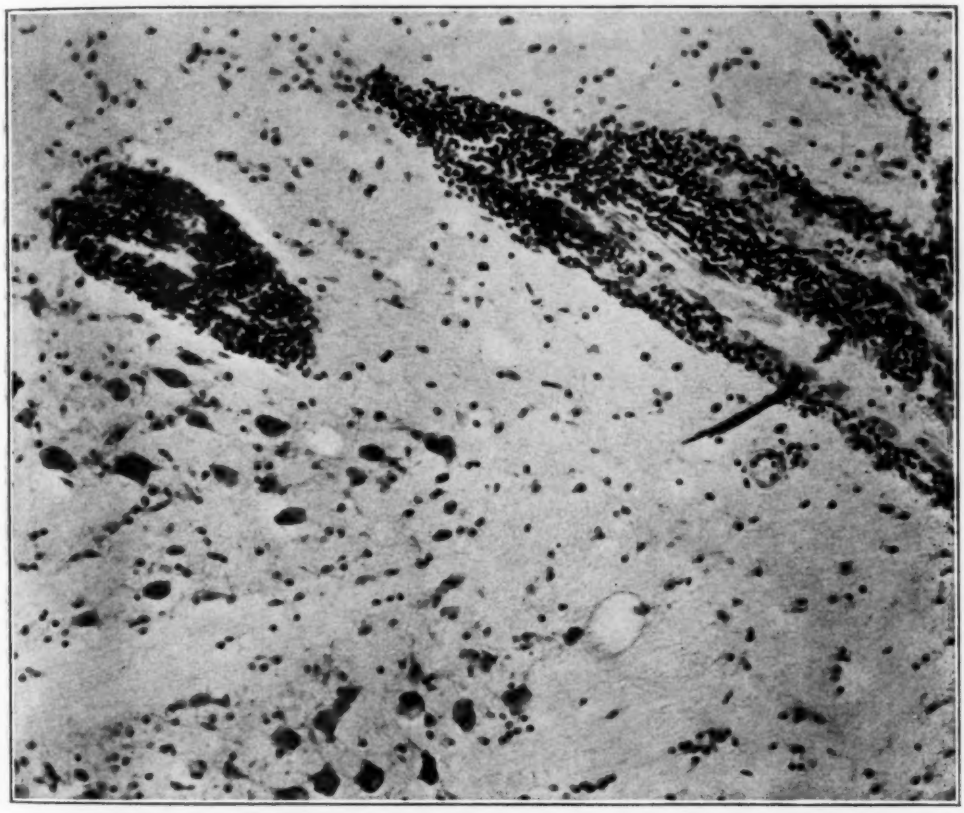

Fig. 4.—Heavy concentration of perivascular cuffing in the substantia reticularis of the medulla. Note the preservation of the nerve cells. Cresyl violet stain; × 220.

Medulla and Pons.—The leptomeninges showed a pronounced infiltration with lymphocytes, especially over the lateral aspects of the medulla and in the immediate vicinity of the fourth ventricle. Engorgement of the adventitial sheaths with hematogenous cells was more pronounced in the medulla and pons than in the cord. A particularly heavy perivascular cuffing was seen in the substantia reticularis, in the region of the nucleus ambiguus, in the dorsal motor nucleus of the vagus nerve and in the floor of the fourth ventricle (figs. 4 and 5). The neuronal

destruction and the microglial proliferation, however, were less pronounced and less severe than in the cord. Actual necrosis of the nerve cells of the vagus except in the nucleus ambiguus and the dorsal motor nucleus was seldom seen. The region of the olives and of the pyramidal tract had completely escaped alteration.

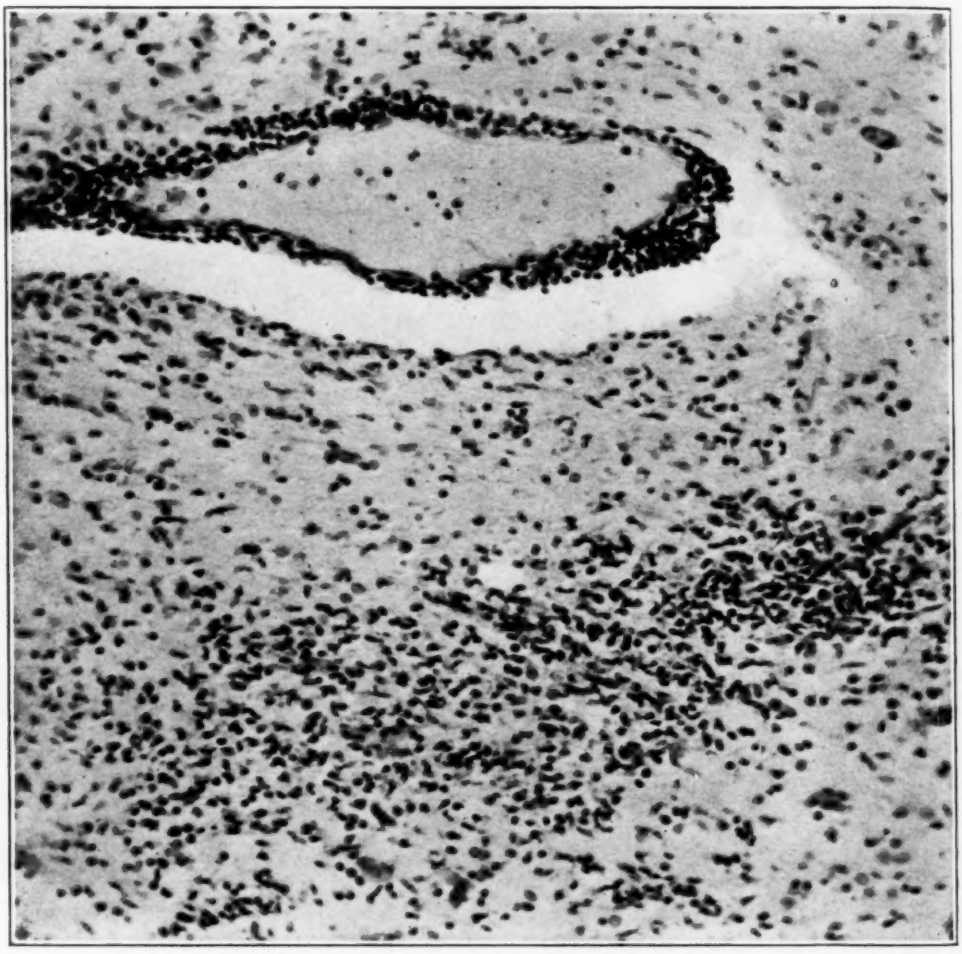

Fig. 5.—Inflammatory changes in the region of the nucleus ambiguus. Note the destruction of nerve cells and the dense proliferation of microglial cells. Cresyl violet stain; × 220.

It is noteworthy that in almost all the cases there were numerous foci of lymphocytes in some of the cranial nerves, being especially pronounced along the vagus.

Midbrain.—Lesions, consisting of dense perivascular infiltration, were more intense in the periaqueductal region and in the substantia nigra than at any other level (fig. 6). As a rule there was little actual

destruction of nerve cells; complete chromatolysis with loss of stainability of the cytoplasm was usually the most advanced change encountered. There were a few disseminated foci of miliary granulomas composed of microglia cells (fig. 7). The leptomeninges, especially those of the interpeduncular region, showed a dense infiltration with lymphocytes (fig. 8).

Basal Ganglia.—Involvement of the hypothalamic nuclei, the corpus striatum and the globus pallidus, was only patchy, irregular and moderate

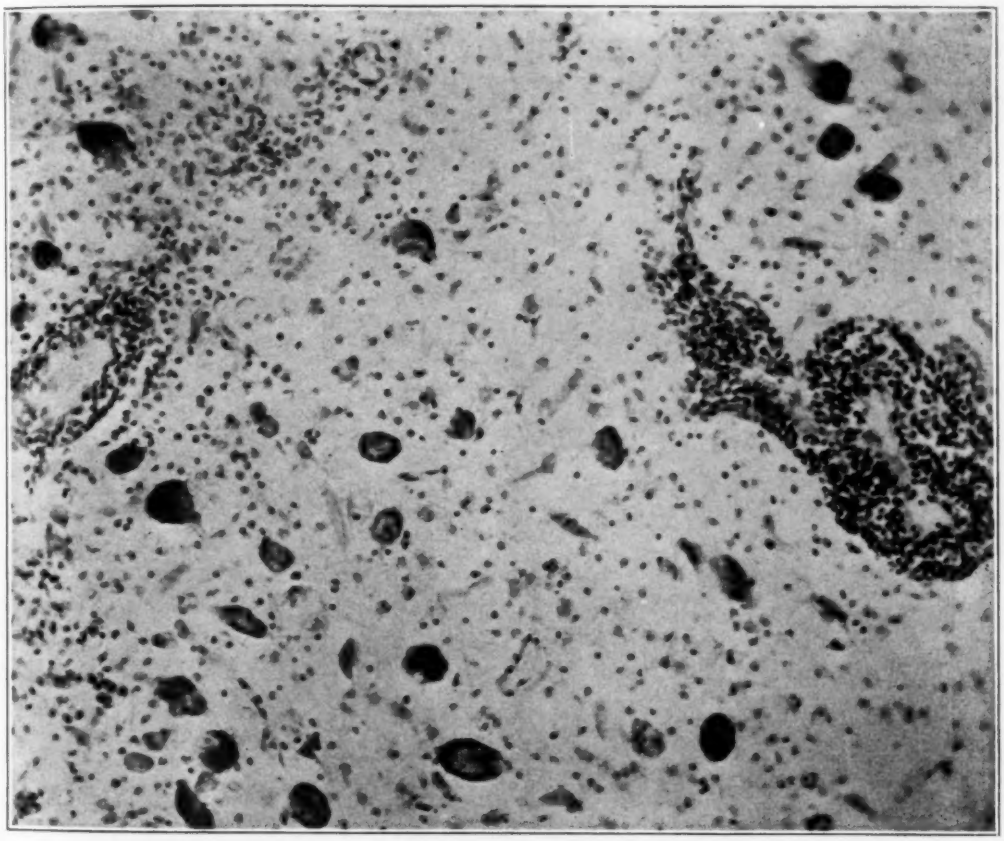

Fig. 6.—Dense perivascular infiltration of the substantia nigra. Note the preservation of nerve cells. Cresyl violet stain; × 260.

in degree. There were a few focal areas of perivascular cuffing, more numerous in the paraventricular regions. Neuronal destruction was not encountered. There were a few disseminated areas of focal accumulations of microglial cells.

Cortex.—In all the cases examined, no alteration of the cortical gray matter was disclosed. The leptomeninges were normal in appearance.

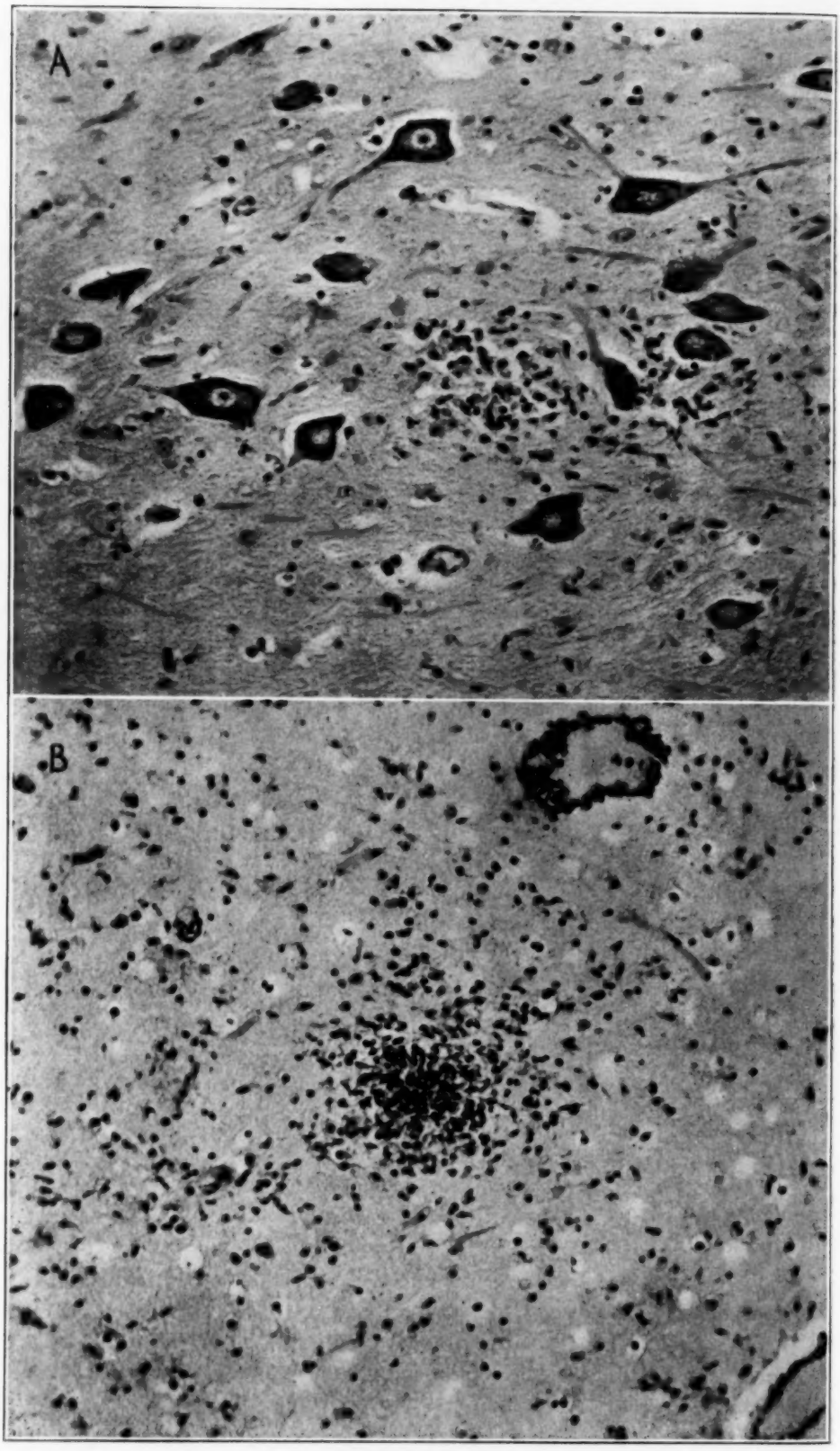

Figure 7

(See legends on opposite page)

Cerebellum.—The dentate nucleus, the roof nuclei and the white matter often showed lesions, consisting of foci of perivascular infiltration and focal accumulations of microglia cells. There was no evidence of severe neuronal destruction.

GENERAL PATHOLOGIC CONSIDERATIONS

Histopathologic changes, as observed in the present series of cases, seem to indicate that the lesions produced in human poliomyelitis are by no means confined to the anterior horns of the spinal cord. No part of the central nervous system entirely escapes damage. The medulla, pons, midbrain and cerebellum are involved to a great extent in every case. Severe inflammatory lesions are especially pronounced in and around the motor nuclei of the medulla (nucleus ambiguus), in the substantia nigra and in the periaqueductal region. There is no denying, however, that in most cases the brunt of the morbid process is borne by the nerve cells of the anterior horn of the spinal cord (which in all cases studied had undergone almost complete destruction).

Whereas the inflammatory process is more intense in the medulla and midbrain, neuronal destruction in these regions is slight as compared with that in the anterior horns of the spinal cord. Necrosis of nerve cells at higher levels is rare. It is justifiable, therefore, to draw the conclusion that there is no direct parallelism between neuronal destruction and inflammatory reactions. This conclusion contradicts the view of a majority of authors. Beneke,[4] Strauss,[5] Wickman,[6] Walter[7] and others have expressed the opinion that damage to nerve cells is proportionate to the degree of inflammatory reaction and that the morbid process of poliomyelitis is characterized by a primary interstitial inflammation with secondary damage to the nerve cells. Such a view is not corrobo-

4. Beneke: Ueber poliomyelitis acuta, München. med. Wchnschr. **57**:176, 1910.

5. Strauss, I.: The pathology of Acute Poliomyelitis and Its Bearing upon the Symptoms of the Disease, Pediatrics **22**:469, 1910.

6. Wickman, I.: Acute Poliomyelitis, translated by J. Maloney, Nervous and Mental Disease Monograph 16, New York, Nervous and Mental Disease Publishing Company, 1913.

7. Walter, R.: Zur Histopathologie der acuten Poliomyelitis, Deutsche Ztschr. f. Nervenh. **45**:79, 1912.

Fig. 7.—*A*, miliary granuloma of the midbrain, composed of a small number of microglia cells (early stage). Note the well preserved nerve cells. Cresyl violet stain; × 260.

B, advanced stage of granuloma formation. Cresyl violet stain; × 260.

rated by the present study. The experimental studies of Hurst,[8] Sabin [9] and others gave conclusive evidence that neuronal destruction is due to direct action of the virus on the nerve cells, and not to inflammatory reaction. The present study leaves no doubt that the infection in monkeys (as described by Hurst[8]) reproduces accurately the essential features of the morbid process in human poliomyelitis.

In all the cases studied the distribution and severity of the inflammatory changes did not correspond with the degree and distribution of the neuronal damage. Whereas the inflammatory changes were most

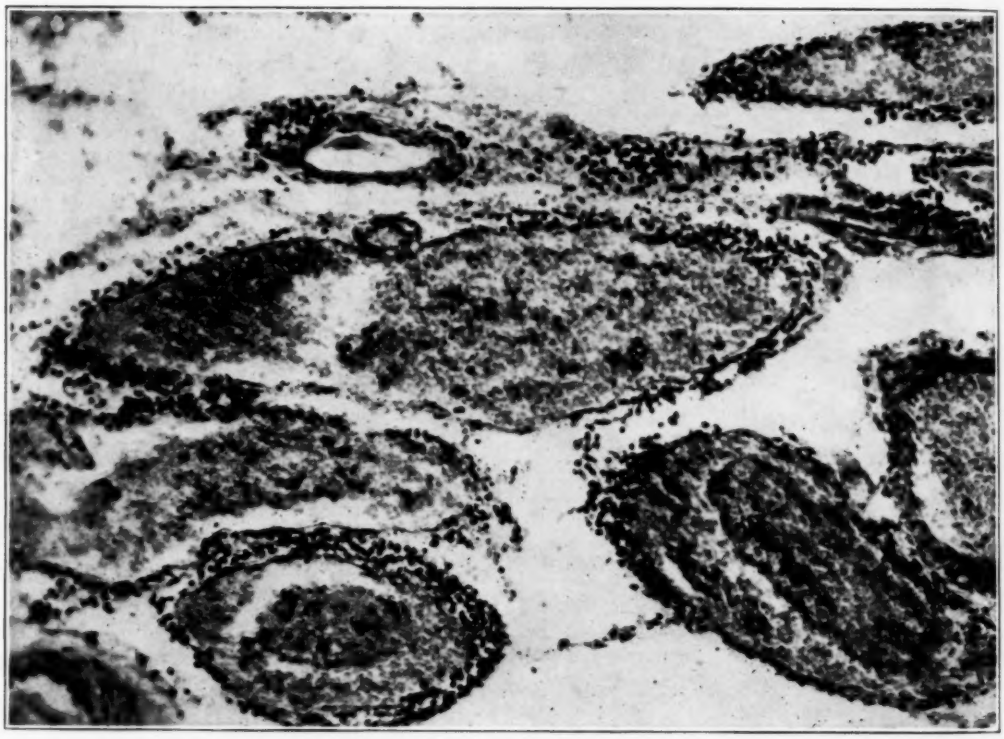

Fig. 8.—Perivascular cuffings of the leptomeningeal vessels of the interpeduncular region. Hematoxylin and eosin stain; × 140.

intense in the midbrain and the medulla, the destruction of nerve cells was only slight and insignificant in this region. On the other hand, in the anterior horns of the spinal cord, where the destruction of nerve cells was almost complete, the inflammatory changes were less noticeable than in the medulla and the midbrain. In short, there is no direct parallelism

8. Hurst, E. W.: Histology of Experimental Poliomyelitis, J. Path. & Bact. **32**:457, 1929.

9. Sabin, A. B.: Pathology and Pathogenesis of Human Poliomyelitis, J. A. M. A. **120**:506 (Oct. 17) 1942.

between degenerative and inflammatory lesions; they are independent phenomena.

Microglial Reaction.—Little reference is made in the literature to the role and significance of microglial reaction in cases of poliomyelitis in man; yet in all the present cases diffuse proliferation of microglia cells presented itself as a striking, predominant tissue reaction.

Under low magnification, the gray matter of the spinal cord manifested itself as very cellular. The bulk of the cells were com-

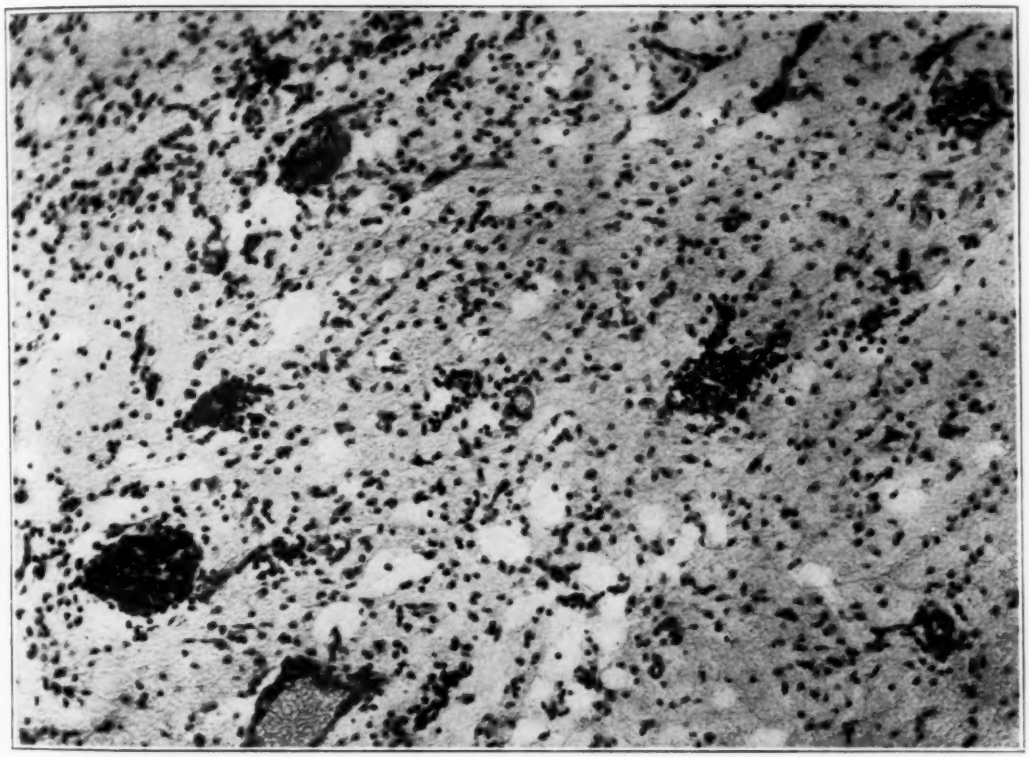

Fig. 9.—Disseminated focal areas of microglial proliferation within the gray matter of the spinal cord; some of the granulomas correspond in position to severely damaged or destroyed nerve cells. Cresyl violet stain; × 160.

posed of a tremendous amount of proliferated microglia cells, which as a rule tended to infiltrate the entire gray matter (fig. 1). Only in those areas in which the neuronal destruction was less severe did some of the microglia cells correspond in position to severely damaged or destroyed nerve cells, whereas others were grouped around small veins and capillaries (fig. 9). In preparations stained with cresyl violet or with hematoxylin and eosin, the nuclei of the microglia cells disclosed a considerable polymorphism and assumed a rod-shaped, oval or irregular outline. The cell bodies were hardly discernible. In sections

stained with the special silver carbonate method of Hortega, the number, arrangement and distribution of the specifically stained microglia cells corresponded with those seen in preparations stained with cresyl violet.

More striking was the focal type of microglial proliferation, characterized by formation of "nodules" or "granulomas." The nodules were widely scattered throughout the gray and the white substance and appeared in cross sections as round or ovoid bodies, composed of compact accumulations of multiform microglia cells (fig. 7). Most of the nodules seemed to be formed around severely damaged or completely destroyed nerve cells.

One of the fundamental problems, the affinity of the virus for the gray matter of the spinal cord, has not yet been solved. There is no real consensus as to the port of entry of the virus and the route traversed on its way to the spinal cord. A study of the distribution of the virus in persons who died of poliomyelitis indicated that the virus is found predominantly in certain regions of the central nervous system and in the alimentary tract (Sabin and Ward [10]). The almost regular presence of the virus in the walls of the pharynx or ileum or in the intestinal contents, and its absence from most other tissues that were tested, suggest (according to Sabin and Ward) that the alimentary tract may be the first site attacked by the virus of poliomyelitis. Sabin [9] indicated that there is a good deal of suggestive evidence that the virus may invade the central nervous system along the fifth, seventh, ninth and tenth cranial nerves from the upper part of the alimentary tract, giving rise to primary bulbar poliomyelitis. Massive inflammatory changes in the medulla and the midbrain, as well as along some of the cranial nerves, as seen in all cases in the present study, seem to corroborate this view. The pronounced concentration of the inflammatory and degenerative processes in the region of the vagal nuclei might be considered suggestive evidence of the possible spread of the virus from the intestine into the central nervous system by way of the afferent and efferent pathways of the vagus.

Movement of virus along nerve structures in the central nervous system of three series of rhesus monkeys after transection of the spinal cord in the midthoracic region was studied by Howe and Bodian.[11] The experiments demonstrated clearly that the interruption of the continuity of the spinal cord, the sympathetic nervous system and the subarachnoid space did not prevent the virus from passing into the rostral

10. Sabin, A. B., and Ward, R.: Natural History of Human Poliomyelitis: Elimination of Virus, J. Exper. Med. **74**:519, 1941.

11. Bodian, D., and Howe, H. A.: Neurotropism and the Genesis of Cerebral lesions in Poliomyelitis: An Experimental Study, Bull. Johns Hopkins Hosp. **68**:58, 1941; Neuropathological Evidence on the Portal of Entry Problem in Human Poliomyelitis, ibid. **69**:183, 1941.

portion of the neuraxis. The authors suspected the participation of the vagus nerve in cases in which sympathectomy had been performed. Examination of serial sections of the brains of 4 animals revealed an unusually severe degree of involvement of the vagal nuclei in the medulla.

SUMMARY

Until recently, acute anterior poliomyelitis was regarded by clinicians and pathologists alike as a disease of the anterior horns of the spinal cord. The present study brings out the fact that no part of the central nervous system entirely escapes damage. The medulla, pons, midbrain, hypothalamus and cerebellum were involved to a great extent in every case.

The literature abounds with controversy concerning whether the damage to nerve cells or the inflammatory process constitutes the primary alteration. In all the cases studied there was no direct correlation between the degenerative neuronal changes and the inflammatory reaction. The view is expressed that they are independent phenomena.

Both diffuse and focal proliferations of microglia cells were noted as striking and predominant tissue reactions in all cases.

The pronounced concentration of the inflammatory and degenerative tissue reactions in the region of the vagal nuclei observed in all the cases provides additional suggestive evidence of the possible spread of the virus from the intestine into the central nervous system by way of the afferent and efferent pathways of the vagus nerve (Sabin).

Cincinnati General Hospital.

PHYSIOLOGY OF BOTULINUS TOXIN

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PREVIOUS studies on the physiology of botulinus toxin have indicated that its action is chiefly on the peripheral rather than the central nervous system.[1] It has also been shown that the nerve trunk and muscle probably are not involved in the poisoning.[2] By a process of elimination it has therefore been reasoned that poisoning occurs at the myoneural junction. On the basis of pathologic studies, however, effects of botulinus toxin on the central nervous system have been described, but there is little agreement among the various reports.[3] Moreover, action of the toxin has been compared to that of curare because the two substances act at approximately the same point in the peripheral nervous system.[1b] This idea has persisted strongly; but, as will be shown later, it appears to be without foundation.

It has been the purpose of the present investigation to obtain additional evidence for localizing the action of botulinus toxin and to investigate the equally important question of the manner in which the toxin produces its effects. Throughout this study, all experiments have been made with type A botulinus toxin, in distinction to the other types. From additional limited experience with types B, C and E toxin, there is no reason to believe that the different types of toxin vary in their action except in their rate of absorption, in speed of destruction in the body and in quantity necessary to produce poisoning.

Data presented on work carried out at Camp Detrick, Md., between August 1944 and October 1945.

1. (*a*) Dickson, E. C., and Shevky, E.: Studies on the Manner in Which the Toxin of Clostridium Botulinum Acts upon the Body: II. The Effect upon the Voluntary Nervous System, J. Exper. Med. **38**:327-346 (Oct.) 1923. (*b*) Edmunds, C. W., and Long, P. H.: Contribution to the Pathologic Physiology of Botulism, J. A. M. A. **81**:542-547 (Aug. 18) 1923.

2. Bishop, G. H., and Bronfenbrenner, J. J.: The Site of Action of Botulinus Toxin, Am. J. Physiol. **117**:393-404 (Nov.) 1936.

3. Dickson, E. C., and Shevky, E.: Botulism: Studies on the Manner in Which the Toxin of Clostridium Botulinum Acts upon the Body; I. The Effect upon the Autonomic (Involuntary) Nervous System, J. Exper. Med. **37**:711-731 (May) 1923.

EXPERIMENTAL METHODS FOR PRODUCING COMPLETE PARALYSIS OF MUSCLE

In previous experimental studies on botulism in animals no investigator has produced complete paralysis, and the data have been obtained from animals only partially paralyzed. In this present work two methods have been used to produce completely paralyzed experimental animal preparations. One of the methods depends on the local action of botulinus toxin when injected into muscle. This has been strikingly demonstrated in recent studies by one of us (M. A. M.).[4] On injecting approximately 1 lethal dose of toxin into the gastrocnemius muscle of a guinea pig and two days later treating the animal systemically with large quantities of antitoxin, it is possible to paralyze completely the gastrocnemius muscle and yet not produce generalized paralysis. The amount of paralysis is determined by measurement of the action potential of the muscle and by measurement of muscular contraction on a kymograph when the sciatic nerve is stimulated. When these measurements are to be made, local anesthesia is produced by sectioning the upper lumbar portion of the spinal cord, with the animal under temporary ether anesthesia. The poisoned muscle may then be studied for as long as forty-eight hours before the animal dies. The unpoisoned gastrocnemius serves as an ideal control.

The second method of producing completely paralyzed preparations is that of keeping a systemically poisoned animal alive until all muscles in the body are paralyzed. This is accomplished by giving artificial respiration to the poisoned animal to offset the effects of respiratory paralysis. Also, vasoconstrictor drugs are given to prevent circulatory collapse. Approximately 1,000,000 rabbit minimal lethal doses of toxin was injected intravenously into each of a series of rabbits. In about one and one-half hours all reflexes in such animals are lost, including the rhythmic nasal reflex of respiration, the corneal reflex, pain reflexes and tendon reflexes. When the animal is lifted in this condition, it is completely flaccid and feels as though it were made of soft rubber. The animal's body becomes colder as time passes, and the final clinical picture is one of profound shock, but the heart continues to beat for several hours.

FURTHER EVIDENCE FOR LOCALIZATION OF BOTULINUS POISONING AT THE MYONEURAL JUNCTION

Action of Botulinus Toxin on the Nerve.—It has been reported that the oscillogram of an excised nerve is not affected by large concentrations of toxin over a period of several hours.[2] In this laboratory, the effect of toxin on the intact nerve was studied by oscillographic methods in two series of experiments.

First, in a series of 5 guinea pigs, equal quantities of toxin were injected in the same animal directly into the left gastrocnemius muscle and into the region around the right sciatic nerve near its exit from the pelvis. Oscillographic studies made by stimulating the sciatic nerve at its point of origin and recording from the muscle demonstrated almost complete paralysis of the left gastrocnemius but no paralysis of the right gastrocnemius. This experiment illustrates that botulinus toxin

4. MacDonald, M. A.: Unpublished data.

has much less effect on the nerve trunk than on the muscle. The action in the muscle, however, might be on the muscle itself, on the nerve endings or on terminal nerve fibrils. It is possible, on the other hand, that the upper portion of the nerve is protected by its sheath and that an action of the toxin would be apparent in the proximal portion of the nerve if botulinus toxin could penetrate to the fiber.

Second, in a series of 8 guinea pigs, one of the gastrocnemius muscles of each animal was paralyzed by the method of local injection previously described. In poisoning the gastrocnemius, 1 cc. of solution of the toxin was injected into the proximal portion of the muscle. Actually, most of this solution then diffused into the popliteal space and up the posterior part of the thigh. In every instance the low thigh muscles themselves showed evidence of at least partial paralysis, and atrophy of some of these muscles occurred after a period of several months. The important point, however, is that the sciatic nerve was bathed in toxin solution within the popliteal space. Oscillograms were made from the sciatic nerve immediately proximal to the gastrocnemius muscle of both the paralyzed and the nonparalyzed side over a period of five to forty-two days after poisoning. The average voltage recorded from the nerve of the paralyzed side was 94 per cent of that recorded from the normal side, or, in other words, approximately the same. At the same time, the action potentials from the paralyzed muscles after stimulation of the sciatic nerve averaged only 21 per cent of the normal value over the period of five to forty-two days after injection.

Briefly, it must be mentioned that in still another series, of 16 guinea pigs, the same quantity of toxin as that usually injected into the muscle was injected into the popliteal space. In these animals the gastrocnemius muscles always exhibited some paralysis, but in these muscles the paralysis never occured as rapidly or as completely as in those muscles which received the toxin directly. Also, when muscles were poisoned directly and oscillograms were obtained during all stages of poisoning, it was noted many times that the action potential of the muscle would disappear but that the action potentials of nerves running adjacent to the muscle electrodes remained of normal value. In these experiments, it was certainly true that the nerves had as good an opportunity to be poisoned as did the muscle itself.

All these experiments tested only the local action of toxin on the nerve, but it is evident that at no time was there impairment of conduction by the nerve; and yet there was no passage of impulse into the muscle. Again, it must be pointed out that the fibrous and myelin sheaths of motor nerves might account for some of the phenomena which have been observed. Regardless of whether this is true, it remains true that quantities of toxin which will not affect the nerve trunk physiologically will cause marked impairment of the passage of impulses from nerve to muscle.

Action of Botulinus Toxin on Muscle.—Study of the muscle itself in botulinus poisoning showed a few changes in its response to direct electrical stimulation. For instance, the threshold of direct stimulation had increased approximately thirty times two days after poisoning. This same increase in threshold occurred in muscles of animals in which the sciatic nerve had been cut for two days. Also, two days after the muscles had been poisoned with botulinus toxin, the contraction as measured on the kymograph decreased to 70 per cent of normal. Here, again, similar results occurred two days after sectioning the sciatic nerve, instead of poisoning the animal. These changes in the muscle, therefore, cannot be ascribed to direct poisoning of the muscle, for the changes take place in muscle denervated by simple mechanical means. On the other hand,

Study of Delay in Conduction at the Sciatic-Gastrocnemius Myoneurol Junction

Animal No.	Dose, M.L.D.	Time, Hr.	Poisoned Leg		Normal Leg	
			Synapse Time, Milliseconds	Action Potential, Millivolts	Synapse Time, Milliseconds	Action Potential, Millivolts
1	1	16	0.60	16	....	..
2	1	16	0.60	10	....	..
3	1	18	0.74	17	....	..
4	1	22	0.74	22	....	..
5	1	22	0.74	4	0.53	32
6	1	23	0.88	13	0.53	29
7	0.5	23	0.67	13	0.56	26
8	0.5	23	Unmeasurable	1	0.46	53
9	0.5	23	1.03	6	0.60	26
10	0.5	24	0.74	13	0.39	45
11	0.5	17	0.82	6	0.39	56
12	0.5	18½	0.74	17	0.39	39
13	0.5	22	0.82	20	0.53	33
14	0.5	22	0.82	9	0.53	30
15	0.5	24	0.60	9	0.46	30
16	0.5	25	0.60	10	0.24	25
Average	0.69	21	0.74	11.7	0.46	35.3

numerous studies on fatigue, tetanizing studies and measurements of impulse conduction failed entirely to reveal any significant changes from normal. Indeed, muscles which were paralyzed for several months actually became fibrotic and lost considerable mass, as though the nerve had been sectioned; but these muscles remained responsive to direct electrical stimulation at all times. In every way, the muscle in botulinus poisoning was found to be comparable to a denervated muscle, and no physiologic changes were observed which would indicate an action of the toxin on muscle other than that of denervation.

Action of Botulinus Toxin on the Myoneural Junction.—With probable elimination of the nerve trunk and the muscle as loci of botulinus poisoning, it appears that the toxin acts directly on the myoneural junction or on the terminal nerve fibrils. The delay in conduction at the myoneural junction in partially paralyzed preparations was studied, as shown in the table, in an attempt to determine in which of these two

sites the toxin produces its effects. These times of delay were determined oscilloscopically by measuring the time required for the impulses to travel down the sciatic nerve and into the muscle fibers. From the total conduction time was subtracted the average time for the impulse to travel down the nerve itself, as determined by a separate series of measurements. Reference to the table shows that there is a considerable increase in the delay of conduction at the myoneural junction in botulinus-poisoned preparations.

Also, by making serial recordings of the action potentials from poisoned muscles on motion picture film at intervals of one minute, it was possible to project the records of these action potentials as a continuous motion picture. In 5 such pictures, showing the change in action potential from normal to complete paralysis, the increasing delay is striking.

This increase in delay does not prove that the toxin acts at the myoneural junction, but it is indicative that this junction is altered in botulinus poisoning. This delay might possibly be in the terminal fibrils, but it is doubtful whether as much delay as that noted could take place in these short fibers.

EFFECT OF DRUGS ON BOTULINUS POISONING

Neostigmine.—Various investigators have found that neostigmine and physostigmine have little, if any gross beneficial effect on botulinus-poisoned animals.[5] Theoretically, if botulinus toxin should act in the same manner as does curare, physostigmine should have a powerful effect in averting paralysis caused by the toxin. A simple experiment, therefore, was designed to prove the validity of these previous reports. Two guinea pigs with approximately 80 per cent paralysis of the gastrocnemius were employed. The gastrocnemius of these animals was stimulated at a rate of four times per second, and contraction of the muscle was recorded on a kymograph. After a control run of five minutes, and while the muscle was still contracting, neostigmine methylsulfate, in a total dose of 0.2 mg., was injected intraperitoneally into each animal over a period of thirty minutes. At the end of this time the animal had gone through all stages of effect of neostigmine, until death occurred from an overdose. Records obtained on the kymograph during these transitional stages showed that neostigmine did not at any time significantly decrease the paralysis.

Acetylcholine.—Because curare prevents contraction of the muscle after intravenous injection of acetylcholine, as well as after stimulation of the nerve,[6] it was desirable to see whether or not this is true of botulinus

5. (*a*) Edmunds, C. W., and Keiper, G. F., Jr.: The Action of Botulinus Toxin, J. A. M. A. **83**:495-502 (Aug. 16) 1924. MacDonald.[4]

6. Brown, G. L.; Dale, H. H., and Feldberg, W.: Reactions of the Normal Mammalian Muscle to Acetylcholine and to Eserine, J. Physiol. **87**:394-424 (Sept. 8) 1936.

toxin. Legs of guinea pigs and rabbits were completely paralyzed by each of the two methods which have been described, and appropriate oscillographic tests were made to be sure that paralysis was complete. In 2 guinea pigs, 30 to 100 micrograms of acetylcholine injected rapidly into the external iliac artery caused a strong contraction of the poisoned leg as well as of the normal (control) leg. In 4 rabbits with paralyzed legs, 10 micrograms of acetylcholine injected similarly produced a strong contraction. The same quantity was necessary to cause contraction of the normal rabbit leg. Therefore, in both guinea pigs and rabbits completely paralyzed muscles still respond to acetylcholine as well as do normal muscles, as measured kymographically. These experiments seem to indicate that acetylcholine is not produced by the end plate in botulinus poisoning. This is not true of curare poisoning.

In several other experiments it was found that nicotine had the same effect on poisoned muscles as did acetylcholine.

ACTION OF BOTULINUS TOXIN ON THE VAGUS NERVE

Several investigators have recorded effects of botulinus toxin on the vagus nerve,[7] but there is some discrepancy in the statements as to whether vagal paralysis or vagal stimulation is most evident. To clarify this matter, the experiment illustrated in figure 1 was performed with 8 rabbits, using pentobarbital anesthesia and artificial respiration maintained through a tracheal cannula. Standard doses of acetylcholine were injected intermittently into the rabbit's ear vein, and standard tetanizing stimuli were applied intermittently to the peripheral end of the cut left vagus nerve. Both these caused decided fall in blood pressure, as recorded from a femoral cannula. An injection of 1,000,000 rabbit minimal lethal doses of toxin was then given intravenously, and injection of acetylcholine and vagal stimulation were repeated at intervals during the remainder of the experiment. In fifty-five minutes stimulation of the left vagus no longer had any effect on the blood pressure. At this point the intact right vagus was cut and stimulated similarly, with an almost imperceptible effect on the pressure. At the end of ninety-five minutes tugging on both vagus nerves, crushing them and electrically stimulating them had no effect whatever.

The blood pressure continued to respond throughout the experiment to injections of acetylcholine, however, and the heart finally ceased beating at the end of the experiment as a result of one of these injections. It is evident, therefore, that the effect of botulinus toxin on the vagus nerve is exactly the same as the effect on skeletal nerves. It appears that the vagus nerve when poisoned with botulinus toxin, like skeletal nerves, fails to produce acetylcholine at its endings.

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7. Bishop and Bronfenbrenner.[2] Dickson and Shevky.[3] Edmunds and Long.[1b]

Only slight, if any, evidence of vagal stimulation by the toxin was present in these experiments. Certainly, the phase of stimulation is not so marked in vagal stimulation of the heart as it has been shown to be in the salivary glands.[7]

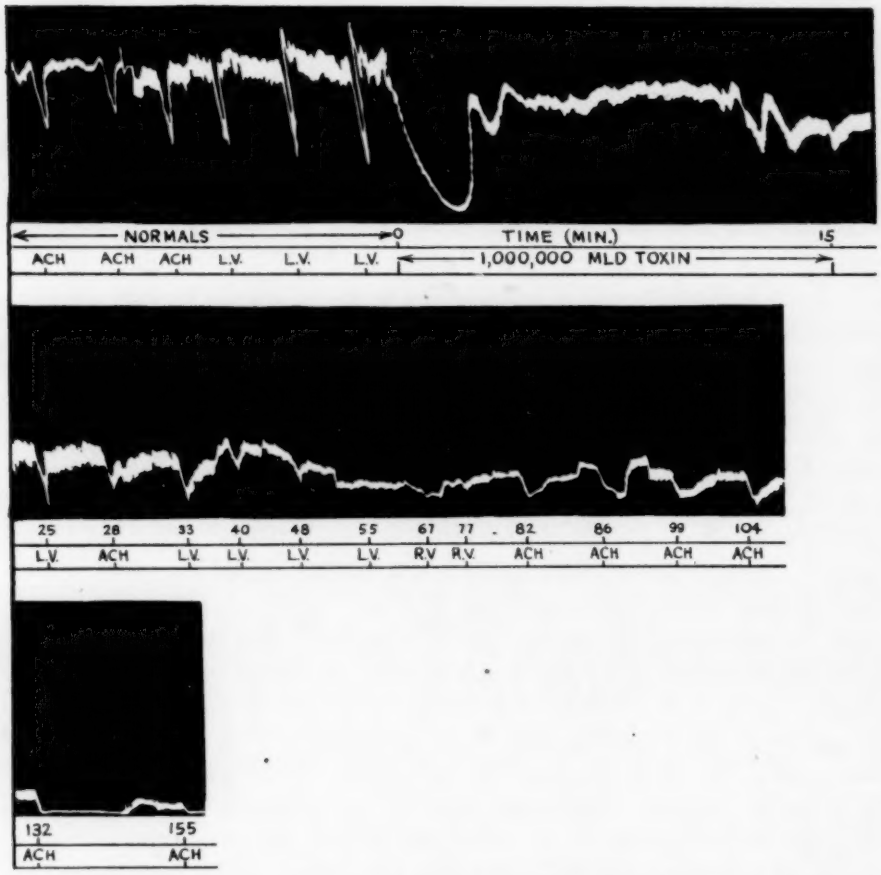
NORMALS
0
TIME (MIN.)
15
ACH ACH ACH L.V. L.V. L.V.
1,000,000 MLD TOXIN
25 28 33 40 48 55 67 77 82 86 99 104
L.V. ACH L.V. L.V. L.V. L.V. R.V. R.V. ACH ACH ACH ACH
132 155
ACH ACH

Fig. 1.—Comparative action of vagal stimulation and injection of acetylcholine on the heart during progressive poisoning with botulinus toxin.

L. V. indicates stimulation of the left vagus nerve with a maximal stimulus of 60 a second; *R. V.*, stimulation of the right vagus nerve with a maximal stimulus of 60 a second, and *ACH*, injection of 0.5 microgram of acetylcholine into the marginal ear vein. Normal recordings were obtained during a thirty minute period prior to injection of toxin into the marginal ear vein.

EFFECT OF BOTULINUS TOXIN ON THE CIRCULATION

When a rabbit is systemically poisoned and death from asphyxia prevented by artificial respiration, an effect of botulinus toxin on the circulation then becomes apparent. It has already been noted that vagal impulses to the heart are inhibited. Theoretically, this should cause a rise in blood pressure, but in a series of 10 animals the pressure actually

7. (*a*) Edmunds and Keiper.[8a] (*b*) Dickson and Shevky.[8]

fell as poisoning proceeded. It was found that vasoconstrictor drugs, particularly paredrine hydrobromide (*p*-hydroxy-α-methylphenylethylamine hydrobromide) were efficacious in preventing this fall in pressure provided these drugs were used early in the experiment. Indeed, 1 animal was kept alive for seven hours, or five and one-half hours after all the skeletal muscles were completely paralyzed. Because paredrine hydrobromide has a powerful vasoconstrictor action on the blood vessels but practically no effect on the heart,[8] it is reasonable to believe that botulinus poisoning causes a peripheral vascular collapse. Also, it appears that the toxin has no direct effect on heart muscle, just as it has no direct effect on skeletal muscle.

The fact that vasoconstrictor drugs have such a powerful effect in maintaining blood pressure probably rules out increased capillary permeability as the cause of lowered pressure. Vasoparalysis, which therefore appears to be the most notable effect that botulinus toxin has on the circulation, might be due, first, to a direct action on smooth muscle; second, to an effect on the sympathetic nervous system, or, third, to an action on the central nervous system. The last of these possibilities seems most likely because of the similarity between synapses in the central nervous system and the nerve endings of skeletal muscle.

EFFECT OF PURE TOXIN ON THE RABBIT

Crude botulinus toxin contains large amounts of impurities carried over from growth mediums. To determine the effect caused by impurities, a rabbit was poisoned with 1,000,000 minimal lethal doses of toxin which had been purified until it was electrophoretically homogeneous and from which pure crystals of toxin had actually been prepared.[9] This animal failed to show any immediate symptoms whatever, but within thirty minutes respiratory paralysis began to appear, and circulatory effects were evident within one hour. The purified preparation of toxin acted precisely as did the nonpurified toxin except that the immediate fall in blood pressure often seen when crude toxin was injected was not present.

USE OF ANTITOXIN IN TREATMENT OF BOTULINUS POISONING

Delayed Treatment.—It has been the impression that antitoxin is of value only as a prophylactic and is of little value once intoxication has begun.[7a] To test this premise, 24 guinea pigs were poisoned by injecting a little over 1 lethal dose of toxin subcutaneously. Two days later, after

8. Altschule, M. D., and Iglauer, A.: The Effect of Benzedrine and Paredrine on the Circulation, Metabolism, and Respiration in Normal Man, J. Clin. Investigation **19**:497-502 (May) 1940.

9. Abrams, A; Kegeles, G., and Hottle, G.: The Purification of Botulinus Type A Toxin, J. Biol. Chem., to be published.

local paralysis at the site of injection was already present and general symptoms were just beginning to appear, 11 animals were treated intraperitoneally with 20 units of botulism antitoxin N.N.R. This was enough to neutralize 20,000 times the amount of toxin given. On further observation of these animals, only 3 of the 11 treated animals died, whereas 12 of 13 of the untreated animals died. This difference indicated forcefully that antitoxin is of value long after exposure to poisoning has taken place, and even after some symptoms of intoxication are present.

Effect of Passive Immunization on the Phenomenon of Local Paralysis from Injection of Botulinus Toxin.—It is of interest from an immunologic point of view to know whether passively injected antitoxin can prevent paralysis due to local injection of toxin into a muscle. Three guinea pigs were passively immunized with 20 units of botulism antitoxin each, and six and one-half hours later 1 minimal lethal dose of toxin was injected into the left gastrocnemius muscle of each animal. On testing these animals by oscilloscopic and kymographic methods previously described, no paralysis could be detected. In nonimmunized animals this amount of toxin injected locally universally produces complete paralysis of the muscle. Therefore, it is concluded that passive immunization does protect against muscular paralysis due to locally injected toxin.

Irreversibility of Botulinus Poisoning with Antitoxin Therapy.—In order to understand the value of antitoxin in treatment, one must know whether or not the poisoned end plate can be restored to normal with antitoxin. In the experiments on delayed treatment, toxin had been circulating in the body for two days, but the nerve endings had been only partially, if at all, poisoned. To determine the value of antitoxin in treatment of the completely poisoned nerve endings, 25 guinea pigs were poisoned locally in the right gastrocnemius muscle with 1 minimal lethal dose of toxin. Two days later tests showed these muscles to be completely paralyzed. The animals were treated at this time with 20 units of botulism antitoxin, enough to neutralize 20,000 times the amount of toxin injected. On studying these poisoned muscles for contraction and action potentials over a period of several months, there was no evidence that the antitoxin per se had any effect on the course of poisoning. During the twenty days immediately following treatment with antitoxin, which should also be the duration of passive immunization with the antitoxin, no animals showed signs of recovery. It appears, therefore, that once poisoning of the nerve endings has occurred antitoxin has no power to reverse the effects of botulinus toxin.

DURATION OF BOTULINUS POISONING

It has long been the belief that if a patient could be kept alive through the acute phases of botulinus poisoning with artificial respiration his

life could be saved.[7a] Therefore it was desirable to know how long the effects of botulinus poisoning last. In discussing the methods of producing completely paralyzed preparations, it was pointed out that by local injection one gastrocnemius of an animal can be completely paralyzed while the major portion of the animal's body remains practically unharmed. By this method the right gastrocnemius muscles of 38 guinea pigs were each poisoned with 1 minimal lethal dose of toxin and the animal protected from systemic effects by administration of 20 units of botulism antitoxin two days later. In each animal the right gastrocnemius muscle was completely paralyzed, but the animals otherwise appeared healthy. These animals were killed and studied at intervals during the

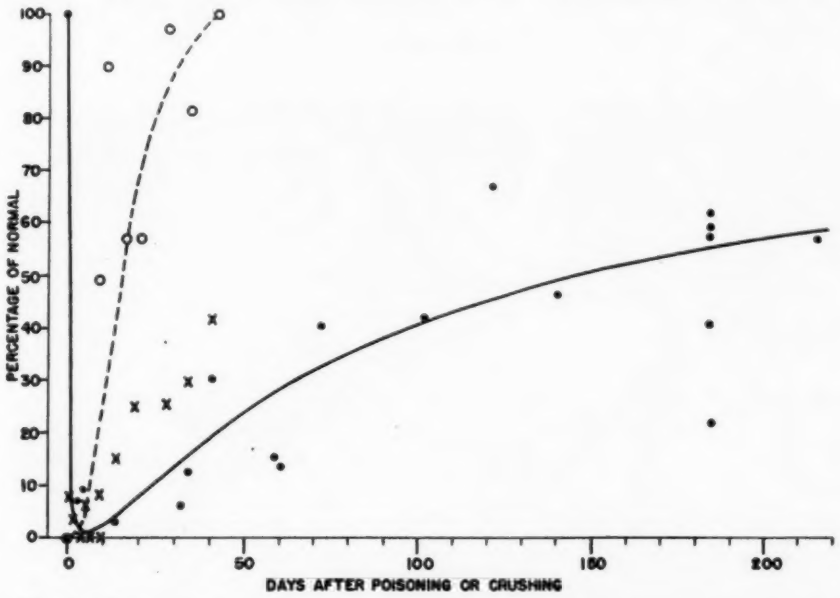

Fig. 2.—Recovery of the action potential in the gastrocnemius muscle of guinea pigs after botulinus poisoning and after crushing the sciatic nerve. The solid line represents poisoned preparations, and the broken line, preparations with a crushed nerve. Circles represent preparations with crushed nerve; dots and crosses, poisoned preparations of two different series.

next year. The muscular contraction and the action potential were recorded from each poisoned gastrocnemius, using the opposite, unpoisoned, gastrocnemius as a control. The solid curve in figure 2 illustrates the recovery of action potential for the next seven months. Recovery of muscular contraction paralleled closely this recovery of action potential. Three animals studied at the end of a year showed approximately 90 per cent recovery. It is hardly possible that any toxin remained in the animal's body during this time, for it must be remembered that enough antitoxin was administered to neutralize 20,000 times the toxin given. This period of one year, therefore, is approximately the time

necessary to repair the damage in guinea pigs caused by botulinus poisoning.

The recovery from botulinus poisoning was found to be approximately ten times as slow as recovery from crushing the sciatic nerve immediately above the gastrocnemius. The latter experiment is illustrated by the broken line in figure 2. Again, it appears from this comparison that the poisoning process is not simply a destruction of nerve fibrils but that it probably has an action at some point which cannot be repaired as quickly as can the fibrils.

HISTOLOGIC STUDIES OF BOTULINUS-POISONED END PLATES

Because toxins which cause semipermanent effects usually produce these effects through morphologic changes, it was anticipated that such

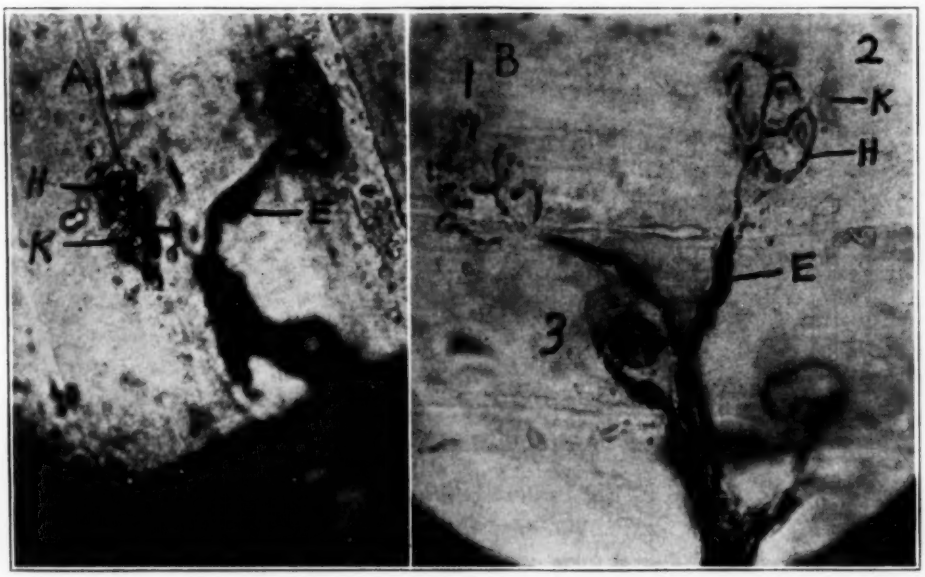

Fig. 3.—Comparison of normal (*A*) and botulinus-poisoned (*B*) end plates; × 300. Note the swelling of poisoned end plates and the absence of granules of Kühne in end plate *1*. End plate *3* shows signs of pyknosis. *K* indicates granules of Kühne; *H*, hypolemmal axon, and *E*, epilemmal axon.

changes would be noted on histologic study of poisoned end plates. The end plates from the poisoned gastrocnemius of 14 guinea pigs were studied with the gold chloride and glycerin mount technic. These gastrocnemius muscles had been poisoned from four days to seven months. In acutely poisoned muscles many swollen end plates were seen, as illustrated in figure 3 *B*, and compared with the normal controls of 3 *A*. Often, considerable granulation of the hypolemmal axon was present, and almost always there were dissolution and disappearance of the granules of Kühne. Occasionally pyknotic end plates were encountered. As the

muscles proceeded toward recovery during the next seven months, the swollen end plates disappeared early, and in their place were seen irregular, darkly staining end plates, which became more nearly normal as time passed. At no time did the end plates disappear. Certain histologic changes, therefore, were observed in the end plates of botulinus-poisoned animals, but these changes were not as definite as had been suspected.

TOXICITY OF BOTULINUS TOXIN

No paper on the physiology of botulinus poisoning would be complete without emphasizing the extremely minute quantity of toxin required to produce poisoning. For instance, the minimal lethal dose for a 20 Gm. mouse is 0.000,000,000,03 Gm. of crystalline toxin.[9] For guinea pigs weighing fifteen times as much the minimal lethal dose is ten times as great; for rabbits weighing 100 times as much it is 100 times as great, and for monkeys weighing 150 times as much it is 300 times as great. In general, except for certain species differences in susceptibility, the lethal dose of toxin varies directly with the weight of the animal. Continuing this reasoning, and considering man to be as susceptible to botulinus poisoning as the monkey per unit weight, the minimal lethal dose for a 70 Kg. man would be approximately 7,000 times the dose for a 20 Gm. mouse. In other words, it would take less than 0.25 microgram of the pure toxin to kill a man. Few, if any, other poisons are known which approach this toxicity.

COMMENT

It appears from this investigation and from previous studies that the action of botulinus toxin is distal to the nerve trunk and yet proximal to the muscle fibers themselves, or, in other words, at the myoneural junction or in the terminal fibrils. The muscle contracts normally on injection of acetylcholine in physiologic amounts. This and several other reasons indicate that there is no basis for the comparison of curare and botulinus toxin. If production of acetylcholine by the poisoned end plate were only diminished, neostigmine should at least partially neutralize the paralysis. For instance, this is true in the case of myasthenia gravis, which has been reported to be caused by a diminished production of acetylcholine.[10] Experiments indicate, however, that neostigmine has little, if any, effect on botulinus poisoning. It appears, therefore, that this poisoning takes place at some point proximal to

10. Harvey, A. M.; Lilienthal, J. L., Jr., and Talbot, S. A.: Observations on the Nature of Myasthenia Gravis: Phenomena of Facilitation and Depression of Neuromuscular Transmission, Bull. Johns Hopkins Hosp. **69**:547-565 (Dec.) 1941; Observations on the Nature of Myasthenia Gravis: The Effect of Thymectomy on Neuromuscular Transmission, J. Clin. Investigation **21**:579-588 (Sept.) 1942.

that at which acetylcholine is produced in the end plate. Likewise, it appears that poisoning follows the all or none principle, for if there were a gradual diminution in production of acetylcholine neostigmine should be of value in treatment.

The histologic changes observed in the poisoned end plate are difficult to evaluate, for Carey [11] has recently shown that many drugs which do not permanently affect the end plates can cause great contortions and changes in their staining characteristics. It cannot be concluded from the histologic studies presented that there are definite structural changes in the end plate, though the poisoned end plates were not observed to be entirely normal. It would be impossible to say that the effect of toxin is simply a destruction of the end plate, for one must remember that vagal endings, which do not have an end plate, are also poisoned.

There are certain features of the physical and chemical manner of poisoning which have been learned. For instance, recovery from poisoning is not reversible with the use of massive quantities of antitoxin. It appears almost as though the living processes of some fundamental element within the nerve ending were destroyed and that recovery must await regrowth of a new element. It is difficult to believe that poisoning of one year's duration could occur without actual morphologic changes. Assuming the toxin to be equally distributed throughout the body and calculating from the molecular weight of approximately 1,000,000,[12] it would take only one tenth of a molecule per end plate to produce death. This minute quantity of toxin necessary to produce poisoning, the duration of poisoning and the physical properties of the toxin[9] all tend to characterize the toxin as a destructive enzyme.

The latent period between administration of toxin and the occurrence of symptoms can possibly be explained on physical grounds alone. The high molecular weight of the toxin makes absorption from the tissues very slow, and diffusion of this molecule into the nerve ending would likewise proceed with difficulty.

In passing, it should be mentioned that symptoms referable to the central nervous system are rarely, if ever, encountered with botulinus poisoning. One might easily expect to find an action of this toxin on the brain because of the physiologic similarity of myoneural junctions and synapses in the central nervous system. There is, however, practically no diffusion of protein molecules of any size, much less those with a molecular weight of 1,000,000, through the blood-brain barrier, a fact which possibly explains why one sees no symptoms referable to the brain.

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11. Carey, E. J.: Studies on Ameboid Motion and Secretion of Motor End-Plates: III., Am. J. Path. **20**:341-393 (March) 1944.

12. Kegeles, G.: Personal communication to the authors.

The comparison of botulinus toxin to tetanus toxin is more than trivial.[13] The two toxins are produced by organisms which are very similar in their morphologic characteristics, and they are produced under similar conditions. Botulinus toxin is a protein, and tetanus toxin is known to have certain protein reactions, though its exact nature is yet unknown. Also, tetanus toxin has been shown to have a local excitatory action at the nerve ending,[14] which is the site of activity of the botulinus toxin. The fact that botulinus toxin has an excitatory phase for the parasympathetic nervous system has already been mentioned. Because of these similarities, one asks oneself many questions regarding tetanus. Does tetanus produce a long-lasting effect, as does botulinus poisoning? Is the effect of tetanus a morphologic change or a chemical fixation of toxin in nerve cells? Would tetanus toxin produce flaccid paralysis similar to that in botulinus poisoning if the animal were kept alive beyond the excitatory phase? The answers to these questions might give one the clue to the successful treatment of tetanus.

Treatment of botulinus poisoning consists of massive doses of antitoxin, the use of artificial respiration and in cases of severe poisoning, the administration of vasoconstrictor drugs. The fact that poisoning lasts for many months makes the results of such treatment discouraging. The use of artificial respiration for several months or longer is not practical, and if a patient is poisoned sufficiently to require vasoconstrictor drugs he will probably die anyway. The only real salvation seems to be the early use of antitoxin in doses greater than 100,000 units of multivalent serum. Though antitoxin has been shown to be of value for guinea pigs as long as two days after poisoning, it is still true that its effect decreases exponentially with time. One must remember that once the toxin has reached the nerve ending and produced its damage this action is irreversible for many months.

SUMMARY

Further evidence is presented which indicates that the principal action of botulinus toxin is probably at the myoneural junction, though possibly in the terminal nerve fibrils.

Neostigmine has little or no effect on botulinus poisoning.

Acetylcholine and nicotine injected intra-arterially still cause contraction of the muscle after botulinus poisoning. With curare poisoning such is not the case. This indicates a fundamental difference between curare and botulinus toxin.

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13. (*a*) Abrams and others.[9] (*b*) Eaton, M. D., and Gronau, A.: Comparative Studies on the Purification of Tetanus and Diphtheria Toxins, J. Bact. **36**:423-432 (Oct.) 1938.

14. Harvey, A. M.: The Action of Tetanus Toxin on Skeletal Muscle, J. Physiol. **95**:30P-31P (April 14) 1939.

Experimental evidence is presented to show that acetylcholine probably is not produced by the end plate in poisoned animals. The effect of botulinus toxin probably also occurs proximal to the point at which acetylcholine is produced.

Botulinus poisoning appears to affect the vagus nerve in the same manner as skeletal nerves.

Botulinus poisoning causes peripheral circulatory failure.

Antitoxin is of value in treatment of botulinus poisoning in guinea pigs when administered as late as two days after poisoning.

Passive immunization with antitoxin prevents local, as well as general, effects of botulinus toxin.

The action of toxin on nerve endings cannot be reversed by massive doses of antitoxin.

A series of animals with poisoned gastrocnemius muscle showed only 60 per cent recovery in seven months and 90 per cent recovery in one year. In a similar series with crushed sciatic nerve, instead of poisoned end plates, 100 per cent recovery occurred in one and one-half months.

Histologic studies of end plates from poisoned animals showed bizarre effects, among which was swelling. These effects could be due either to altered activity or to actual structural changes within the end plate.

The long period of recovery and the degree of irreversibility of botulinus poisoning in the end plate discourage belief in the possibility of future improvements in clinical treatment.

Major George Hottle and Lieut. Adolf Abrams furnished the purified preparations of toxin. Cpl. Dellas Cosby assisted in this study.

Massachusetts General Hospital, Boston.

Receiving Hospital, Detroit.

MENINGEAL GLIOMATOSIS

A Study of Forty-Two Cases

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THE TERM "meningeal gliomatosis" has been adopted for the title of this study to designate involvement of the leptomeninges by tumors of neuroectodermal origin, in contradistinction to those tumors arising from the mesodermal elements. The terms "gliomatous meningitis" and "tumorous meningitis" erroneously imply an infective process, and for this reason the more descriptive term "meningeal gliomatosis" was chosen.

This study consisted of a review of the gliomas observed at the Mayo Clinic during the period from 1922 to 1942, inclusive, and concerned the finding of metastatic implantations from these gliomas to the leptomeninges of the brain and the spinal cord and the ependyma of the ventricular system. This study was primarily concerned with those gliomas which had established themselves in multiple sites and were responsible for a generalized involvement of the leptomeninges.

Although the earlier literature contains many references to tumors of the central nervous system which had produced local or extensive invasion of the leptomeninges, methods for a more exact classification of such neoplasms have only recently been in use.

Leusden,[1] has been credited as the first to describe an instance of diffuse involvement of the leptomeninges by a tumor, which he termed "gliosarcoma." In 1907 Spiller [2] described an ependymoma of the fourth ventricle with diffuse involvement of the leptomeninges. To our knowledge, this was the first established instance of meningeal gliomatosis.

From the Department of Neurosurgery, the Mayo Foundation (Dr. Polmeteer), and the Section on Pathologic Anatomy , the Mayo Clinic (Dr. Kernohan).

Abridgment of a thesis submitted by Dr. Polmeteer to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Neurosurgery.

1. Leusden, P., cited by Schuberth.[4]

2. Spiller, W. G.: Gliomatosis of the Pia and Metastasis of Glioma, J. Nerv. & Ment. Dis. **34**:297-302 (May) 1907.

Even as recently as 1924, the condition in many cases reported as "sarcomatosis of the meninges" was in reality "gliomatous" in nature. Bailey and Cushing,[3] who made a special study of the medulloblastoma group of gliomas, demonstrated that cells formerly considered sarcomatous were definitely glial and that true "sarcomatosis of the meninges" was extremely rare.

In 1926 Schuberth[4] carefully reviewed the literature in regard to sarcomatosis and gliomatosis involving the leptomeninges and reported 76 cases, in 39 of which the patients had been under his own care.

In 1931 Cairns and Russell[5] described 8 cases of intracranial and spinal metastasis encountered in 22 consecutive cases of primary cerebral glioma in which necropsy was done. They expressed the opinion that this condition was much more common than had previously been considered.

In this study, we have used the classification of gliomas proposed by Bailey and Cushing. We found 42 instances in which there was generalized meningeal gliomatosis. In 20 of these cases the tumor was a medulloblastoma; in 6, glioblastoma multiforme; in 5, ependymoma; in 5, of the oligodendroglioma group; in 3, astrocytoma; in 2, retinoblastoma, and in 1, a pinealoma.

These implants were studied particularly with reference to proliferation of connective tissue and capillaries and to focal degeneration. The formation of connective tissue in the metastatic implants, which probably represents a reaction of the leptomeninges, was obvious only in the less rapidly growing gliomas, such as the astrocytomas and oligodendrogliomas. However, in 1 case of medulloblastoma an abundance of connective tissue was identified in the metastatic growth. Capillary proliferation in the implants was most prominent in the more malignant varieties of glioma, such as glioblastoma multiforme and retinoblastoma. Occasionally we observed proliferation of the walls of the blood vessels similar to that observed in the parent tumor, especially in cases of glioblastoma multiforme. Regions of degeneration, also, were frequently observed in the metastatic implantations from the more rapidly growing gliomas, especially the retinoblastoma and the glioblastoma multiforme. More rarely, slower-growing gliomas may have regions of necrosis.

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3. Bailey, P., and Cushing, H.: A Classification of the Tumors of the Glioma Group on a Histogenetic Basis with a Correlated Study of Prognosis, Philadelphia, J. B. Lippincott Company, 1926.

4. Schuberth, O.: Ueber diffuse Sarkomatose und Gliomatose in den Meningen des zentralen Nervensystems, Deutsche Ztschr. f. Nervenh. **93**:34-60, 1926.

5. Cairns, H., and Russell, D. S.: Intracranial and Spinal Metastases in Gliomas of the Brain, Brain **54**:377-420 (Dec.) 1931.

MEDULLOBLASTOMA

The neoplasm which was given the name "medulloblastoma" by Bailey and Cushing [6] is primarily a midline cerebellar tumor of childhood, protruding into or filling the fourth ventricle but rarely adhering to its floor or invading the medulla oblongata. Medulloblastoma is generally considered a fairly rapidly growing glioma.

The ability of this tumor to become disseminated by the circulation of the cerebrospinal fluid and implanted widely throughout the subarachnoid space has been recognized for some time. Bailey and Cushing, in a study of 400 cases of gliomas, encountered 29 cases of medulloblastoma in 1 of which the neoplasm had led to widespread meningeal gliomatosis. However, it was thought from clinical evidence that there had been secondary implantations in the leptomeninges of the spinal cord in 3 other instances. In 1 of these cases this assumption was verified subsequently by Elsberg.[7]

We found that medulloblastoma was the form of glioma most frequently responsible for meningeal gliomatosis. It occurred in 20 of a series of 42 cases (47.6 per cent). The average age of the patients was 15.7 years. Nineteen of these gliomas originated in the cerebellum, while 1 arose in the left frontoparietal area of the cerebrum. The particles of tumor followed the pathways of the cerebrospinal fluid, became implanted and grew either as small disks or as a continuous sheet, involving most of the cranial nerves, the spinal cord and the cauda equina (figs. 1 and 2). The extent of spread varied, but some degree of leptomeningeal invasion was rarely absent.

The microscopic appearance of the medulloblastomas was characteristic. They were cellular tumors. Many of the cells were carrot shaped, contained oval or oat-shaped nuclei and were more or less closely packed together, forming small rings, or segments of a larger circle, and thus producing "pseudorosettes." When sections were suitably stained, the clear space in the center of these groups of cells was observed to be occupied by the projections of the carrot-shaped cells. Neurocytes, astrocytes and, occasionally, spongioblasts could be demonstrated in the tumors.

The microscopic structure of the metastatic implants (fig. 3) from the medulloblastoma was similar to that of the parent tumor. We frequently demonstrated "pseudorosettes" more readily than in the primary tumor. Capillary and connective tissue proliferations, which were not

6. Bailey, P., and Cushing, H.: Medulloblastoma Cerebelli: A Common Type of Midcerebellar Glioma of Childhood, Arch. Neurol. & Psychiat. **14**:192-223 (Aug.) 1925.

7. Elsberg, C. A.: Tumors of the Spinal Cord: The Symptoms of Irritation and Compression of the Spinal Cord and Nerve Roots; Pathology, Symptomatology, Diagnosis and Treatment, New York, Paul B. Hoeber, 1925, p. 161.

prominent in the primary growths, formed a rather constant feature of the metastatic growths. Capillary proliferation in the metastatic implantations was observed in 18 of the 20 cases studied. Such an adequate blood supply probably was responsible for the infrequency with which regions of degeneration and cyst formations were encountered. Degen-

Fig. 1.—Metastatic implants in the leptomeninges of the lower thoracic and the lumbar segments of the spinal cord and cauda equina from a medulloblastoma located in the cerebellum.

erative changes in the metastatic growths were observed in only 1 instance.

In 15 of the 20 cases of medulloblastoma studied in our series, the neoplasm invaded the leptomeninges and produced an overgrowth of

the connective tissue. It was rare that sufficient reticulum existed in the medulloblastoma to make its differentiation from sarcoma difficult.

GLIOBLASTOMA MULTIFORME

Glioblastoma multiforme comprises more than a third of the gliomas occurring in the adult; it occurs in the cerebrum and is invariably the most rapidly growing of the neoplasms derived from the glial cells.

Metastasis of this type of glioma through the cerebrospinal fluid has been recognized only in recent years. Cairns and Russell, in their excellent monograph, recorded only 1 case of glioblastoma multiforme in their series of 8 cases of spinal and intracranial metastasis. Elvidge, Penfield and Cone [8] encountered 55 cases of this tumor in their series of

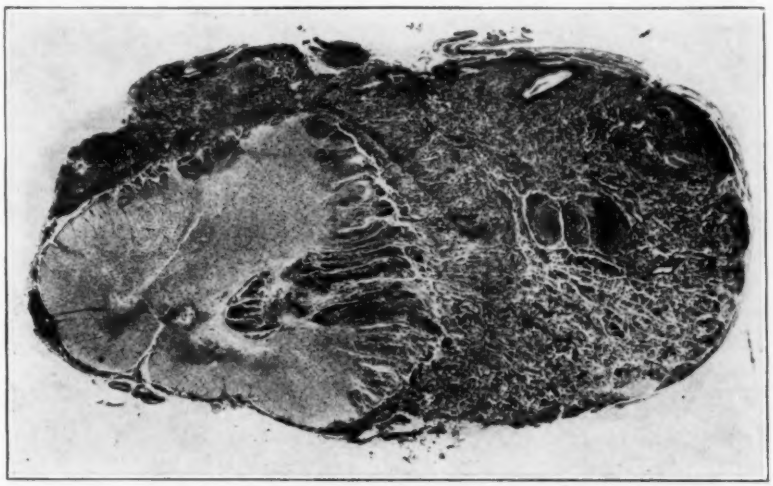

Fig. 2.—Cross section of the upper thoracic segment of the spinal cord, demonstrating the pronounced compression and invasion of the spinal cord by a metastatic tumor, which completely filled the subarachnoid space. The primary tumor was a medulloblastoma of the cerebellum. Hematoxylin and eosin; × 9.

210 verified cases of glioma, or in 26 per cent of the cases studied. They estimated that meningeal involvement by the primary growth occurred in at least 8 per cent of the cases.

In our series of 42 cases of meningeal gliomatosis, we found 6 cases of the glioblastoma multiforme type (14.3 per cent). Each of the tumors was primary in the cerebral hemispheres. Two of the patients were children. The tumor seemed to advance along the principal tracts and frequently spread from one hemisphere to the other across the corpus callosum. The cut surface of the tumor had a characteristic appearance.

8. Elvidge, A.; Penfield, W., and Cone, W.: The Gliomas of the Central Nervous System: A Study of Two Hundred and Ten Verified Cases, A. Research Nerv. & Ment. Dis., Proc. (1935) **16**:107-181, 1937.

It was variously colored—gray, gray-brown, yellow or red, or a combination of these colors—the result of numerous regions of degeneration with old and recent hemorrhages. Occasionally this tumor was in part cystic.

The microscopic study of glioblastoma multiforme revealed considerable polymorphism of cells, unusual vascular changes and regions of necrosis. There was no type of cell which could be regarded as characteristic; however, cells of the spongioblastic, astroblastic and astrocytic types were present. The most common cell seen, which was small and spindle shaped, was most probably an anaplastic form of the astrocytic series. Giant cells, often multinucleated, were invariably present, and

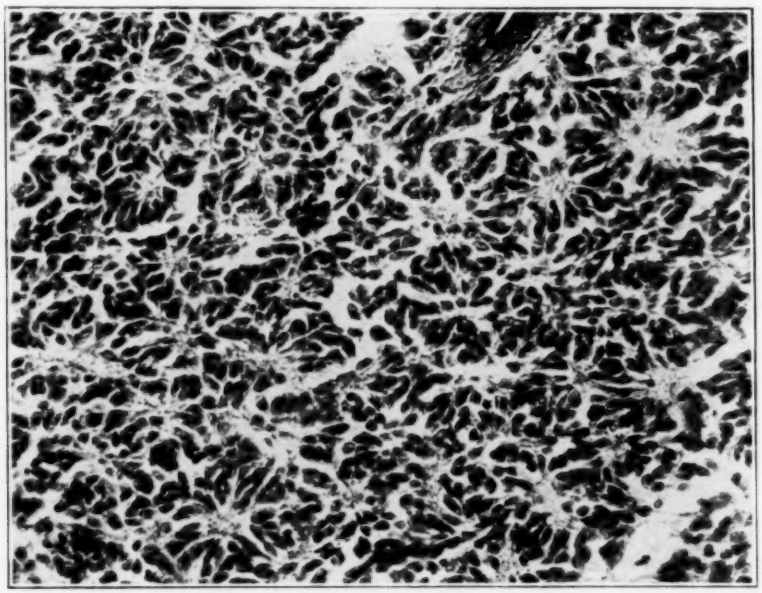

Fig. 3.—Implant in the leptomeninges of the upper cervical segment of the spinal cord from a medulloblastoma originating in the vermis of the cerebellum. This tumor is a typical medulloblastoma. Hematoxylin and eosin; × 295.

numerous mitotic figures were always observed in this tumor. Blood vessels were numerous but quite abnormal in structure. The walls were composed of an abundant endothelial lining supported by a band of fibrous tissue, which often was hyalinized. There was a peculiar overgrowth of the endothelium, which at times became so great that it occluded the vascular lumen, while proliferation of the connective tissue of the adventitia was invariably present. The narrowing or occlusion of the lumen had presumably led to the regions of necrosis.

The histologic structure of the metastatic growths was almost identical with that of the primary tumor; however, capillary proliferation and regions of degeneration were prominent features. There was also considerable local invasion of the adjacent structures by these gliomas.

EPENDYMOMA

In 1907 Spiller reported 1 of the earliest recorded cases of meningeal gliomatosis originating from an ependymoma. This tumor originated in the fourth ventricle and spread to involve the leptomeninges of the brain and spinal cord.

In our series of 42 cases, we observed 5 instances in which meningeal gliomatosis was the result of metastasis from an ependymoma (11.9 per cent). In classifying these tumors, Bailey and Cushing's classification and Kernohan and Fletcher-Kernohan's [9] subdivisions of the ependymoma group were used. Three of the ependymomas of our series were of the cellular type. Two of these showed acinar-like arrangement in one or another portion. Another tumor was classified as a myxopapillary type of ependymoma, and the fifth, as an ependymoblastoma.

The most common intracranial site for the location of the primary ependymoma is the floor of the fourth ventricle. Kernohan and Fletcher-Kernohan studied 109 ependymomas, 54 of which originated intracranially. Of these, 32, or about 60 per cent, were observed to arise from the floor of the fourth ventricle. Cushing [10] found that the 25 ependymomas in his series constituted approximately 3.6 per cent of the 687 classified gliomas. Nineteen of these tumors (76 per cent) originated from the floor of the fourth ventricle, whereas the 6 other tumors (24 per cent) arose from the ependyma of the lateral or the third ventricle. We found that in our present study 2 ependymomas originated from the floor of the fourth ventricle. Another arose in the third ventricle, and 2 represented intramedullary tumors of the spinal cord.

Ependymoma represents the most common variety of intramedullary neoplasms of the spinal cord. This glioma was present in 51 per cent of the cases of intramedullary tumors of the spinal cord studied by Rasmussen, Kernohan and Adson.[11] One of the intramedullary ependymomas of our series originated in the cervical and the other in the thoracic portion of the spinal cord. Both were associated with syringomyelia (fig. 4).

On gross examination, the ependymomas were pale pink or flesh colored, encapsulated, firm and nodular. There was evidence of deposits of calcium and of cyst formation in 1 instance.

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9. Kernohan, J. W., and Fletcher-Kernohan, E. M.: Ependymomas: A Study of One Hundred and Nine Cases, A. Research Nerv. & Ment. Dis., Proc. (1935) **16**:182-209, 1937.

10. Cushing, H.: Intracranial Tumours: Notes upon a Series of Two Thousand Verified Cases with Surgical-Mortality Percentages Pertaining Thereto, Springfield, Ill., Charles C Thomas, Publisher, 1932.

11. Rasmussen, T. B.; Kernohan, J. W., and Adson, A. W.: Pathological Classification, with Surgical Consideration, of Intraspinal Tumors, Ann. Surg. **111**:513-530 (April) 1940.

The ependymomas which we studied were classified according to four types of ependymoma first described by Kernohan and Fletcher-Kernohan. These were papilloma choroideum and myxopapillary, epithelial and cellular ependymoma.

The myxopapillary type of ependymoma is also known as the papillary ependymoma and is similar in many respects to the papilloma of the choroid plexus. One of us (J. W. K.) had previously chosen the more descriptive term "myxopapillary ependymoma," instead of "papillary ependymoma," because of the presence of a large amount of mucus within the stroma of the papillary projections of these tumors which was not

Fig. 4.—Cross sections of the cervical and thoracic portions of the spinal cord, showing the extent of the syringomyelic cavity, which was associated with an intramedullary ependymoma of the eighth cervical segment. *A* indicates the cervical portion above the tumor; *B*, the cervical portion below the tumor; *C*, the high thoracic region, and *D*, the low thoracic region of the cord.

a secretion of the ependymal cells, such as is seen in the cells of the papillomas of the choroid plexus, but represented a myxomatous degeneration of the connective tissue cores of the papillae.

We found only 1 case of myxopapillary ependymoma in our series. The histologic structure of the tumor was typical. The ependymal cells were of the high cuboidal type and had a short, heavy process, which was attached to the connective tissue core of the papilla. The oval nuclei of the cells were large and contained several chromatin granules.

Mitotic figures were not observed. We did not note blepharoplasts in the cytoplasm of these ependymal cells.

Two of our tumors were epithelial ependymomas, both of which occurred in conjunction with the cellular type of ependymoma. The ependymal cells, which were arranged to form canals, resembled those of the central canal of the spinal cord (fig. 5). The cells were not vacuolated or ciliated and contained no mucus. The peripheral ends of the cells usually terminated in a heavy process, which projected into the surrounding tissue. Occasionally these processes became attached to the connective tissue of a nearby blood vessel. The nuclei of these ependymal cells were usually large and elongated. Mitotic figures were not observed.

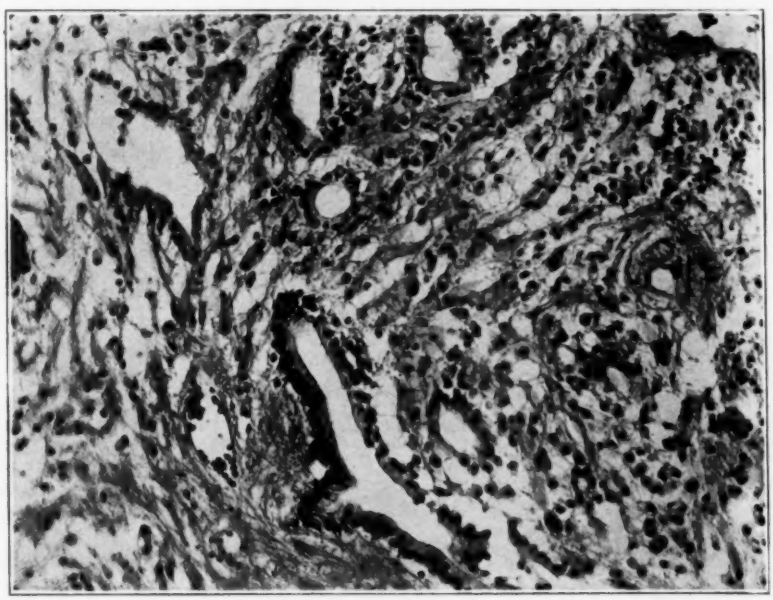

Fig. 5.—One of the epithelial portions of a mixed epithelial and cellular intramedullary ependymoma. The ependymal cells are arranged as canals, which resemble the central canal of the spinal cord. Hematoxylin and eosin; × 145.

The cellular type of ependymoma was the most common variety of ependymoma in our series. The prominent histologic characteristic of the cells of this tumor was their similarity to the astroblasts; however, the nuclei and chromatin granules of the ependymal cells were large, and the tumor cells had no affinity for the gold of Cajal's gold chloride–mercury bichloride (sublimate) impregnation. Occasionally the cells of the tumor had processes which terminated in the neighborhood of a blood vessel. More frequently one or several processes of these cells extended toward a common center, in which no blood vessel was present, thus forming a "pseudorosette." Neuroglial fibrils were not formed by the ependymal cells, and blepharoplasts were not seen. The nuclei of these

ependymal cells were round or oval, and only occasionally were mitotic figures observed. Deposits of calcium were found in 1 of these tumors.

The microscopic structure of the metastatic implantations from the ependymomas closely resembled that of the parent tumor. The metastatic growths were comparatively benign, and we observed only a minimal amount of local infiltration of the surrounding cerebral and spinal tissues. There was little proliferation of connective tissue and no local degenerative change in these metastatic implants. Deposits of calcium were observed in 1 of the ependymomas that we studied, but not in the metastatic growths.

The term "ependymoblastoma" was first proposed by Bailey and Cushing to designate tumors of the ependymoma group of gliomas which were composed primarily of ependymal spongioblasts. In our series, this tumor was found in 1 instance (2.4 per cent).

This ependymoblastoma on gross examination, was pale, flesh colored and firm and appeared to invade the surrounding tissues of the brain more readily than the ependymomas. The metastatic growths from this tumor showed local infiltration of the surrounding cerebral structures.

The ependymoblastoma was more malignant than any of the ependymomas. Histologic examination revealed that the cells of the tumor were slightly larger than those of the ependymomas, and the nuclei were of greater size in proportion to the amount of cytoplasm of the cells. The microscopic appearance was typical and was characterized by the predominance of the ependymal spongioblasts. The nuclei of these cells were elongated or oval and were arranged in "rosette" formation around the numerous thin-walled blood vessels. Mitotic figures were observed commonly.

The histologic structure of the metastatic growths from the ependymoblastoma was similar to that of the primary tumor but differed from the structure of the implants of the ependymoma in showing a greater degree of malignancy.

OLIGODENDROGLIOMA

Bailey and Cushing were the first to recognize and classify the oligodendroglioma as a tumor of the central nervous system which was composed almost exclusively of oligodendroglial cells. They found 9 of these tumors in a series of 254 classified gliomas. Later, Bailey and Bucy [12] proved the presence of oligodendroglia in these neoplasms by detailed histologic studies and reported 6 tumors observed subsequent to those originally described by Bailey and Cushing. Cushing found 27 oligodendrogliomas in a series of 687 classified gliomas (3.9 per cent),

12. Bailey, P., and Bucy, P. G.: Oligodendrogliomas of the Brain, J. Path. & Bact. **32**:735-751 (Oct.) 1929.

none of which produced generalized meningeal involvement. In 1929 Cairns [13] was the first to describe an instance of metastasis from this type of glioma through the cerebrospinal fluid. He reported the surgical removal of an oligodendroglioma originating in the frontal lobe of the right cerebral hemisphere, which, three and a half years later, implanted itself in the fourth ventricle and in the occipital horn of each lateral ventricle. In our series of 42 cases, there were 5 instances in which these gliomas (including the oligodendroblastomas) produced generalized gliomatosis of the meninges (11.9 per cent).

Oligodendroglioma is predominantly a tumor affecting adults. For the most part, it originates in the cerebral hemispheres of the brain and in the spinal cord. All the oligodendrogliomas reported by Cushing originated in the cerebral hemispheres. In 25 of the cases (92 per cent) the patient was an adult. We found 2 cases of oligodendroglioma. In 1 case the tumor was situated in the temporal lobe of the right cerebral hemisphere of a man aged 37. In the other the glioma was located in the lower portion of the pons and the medulla of a woman aged 32.

On gross examination, the oligodendrogliomas were observed to be large, moderately firm and reddish gray, with some deposits of calcium. At times there were small regions of degeneration; cyst formation and hemorrhages were observed. Both these tumors seemed well demarcated from the surrounding tissue of the brain, but definite capsules were not present in either instance.

The microscopic features of the oligodendrogliomas were characteristic. These tumors presented a cellular and uniform appearance, with practically no stroma. The edges of the tumors, which macroscopically had seemed so well demarcated, were not sharply defined on histologic examination and blended into the surrounding tissue of the brain. The nuclei of the cells of these gliomas were small, round and regular in size and shape and contained a heavy network of chromatin. When the neoplastic cells were stained with hematoxylin and eosin, the cytoplasm appeared scanty and indistinct and formed the typical "halo" around the small, deeply stained nucleus. The majority of these nuclei, which were smaller than those of the other gliomas, were almost perfectly round and resembled lymphocytes. Mitotic figures were rarely observed. When the cells of these tumors were impregnated successfully by the Hortega silver carbonate method, the nuclei were lightly stained and the cell outline was heavily impregnated. The majority of the cells were packed closely together in a "pavement-like" arrangement, giving them the typical "honeycomb" appearance.

13. Cairns, H.: A Study of Intracranial Surgery, Medical Research Council, Special Report Series, no. 125, London, His Majesty's Stationery Office, 1929, p. 15.

Astrocytes, as well as ependymal cells, were identified in both these tumors. The implants from these gliomas resembled the primary tumors except that the stroma was somewhat more prominent. Regions of degeneration also were observed in these metastatic growths. At times, the tumor blended so uniformly into the adjacent cerebral and spinal tissues that it was difficult to determine accurately the true limits of the metastatic growths.

The term "oligodendroblastoma" has been used to designate the more actively growing types of oligodendroglioma. In our series we found 3 instances in which the oligodendroblastoma was responsible for generalized meningeal gliomatosis (7.1 per cent). Two of these tumors were primary in the cerebral hemisphere, while the third was an intramedullary tumor of the spinal cord.

The cerebral tumors, on gross examination, were grayish red, contained no deposits of calcium and blended uniformly into the surrounding brain. Spinal metastasis was not observed. On histologic examination we observed that these tumors were similar in most respects to the oligodendroglioma but were more malignant; the nuclei of the cells were larger, and the cytoplasm was more readily visible. Mitotic figures were a prominent feature of these tumors.

The intramedullary tumor of the spinal cord which we studied was an oligodendroblastoma of the eighth cervical segment. The cells of this tumor extended through the cerebrospinal fluid and were implanted extensively throughout the subarachnoid space. The leptomeninges of the entire spinal cord and cauda equina, the base of the brain and the cerebral hemispheres were involved by this process of gliomatosis. The microscopic and macroscopic appearance of the spinal oligodendroblastoma was similar to that of the cerebral tumors. The local infiltrations into the cerebral and spinal structures were more evident in the oligodendroblastomas than in the oligodendrogliomas.

ASTROCYTOMA

In the majority of series of verified intracranial tumors, the astrocytomas form one of the largest subdivisions of the glioma group. These tumors may occur anywhere in the cerebrospinal axis and may be solid or cystic. The solid type of tumor is very firm and comparatively avascular and usually originates in the subcortical substance of the cerebral hemispheres, rarely extends to the surface and is covered by the flattened convolutions of the brain. Most astrocytomas of the cerebellum are cystic.

In 1930 Russell and Cairns [14] reported the first instance of meningeal gliomatosis from an astrocytoma. This glioma originated in the

14. Russell, D. S., and Cairns, H.: Spinal Metastases in a Case of Cerebral Glioma of the Type Known as Astrocytoma Fibrillare, J. Path. & Bact. **33**:383-391 (April) 1930.

right thalamus and metastasized widely in the subarachnoid space, forming metastatic implantations in the leptomeninges of the entire spinal cord. Doubts concerning this observation were expressed at first by a few authors. However, it was confirmed in 1931 by Cairns and Russell. With the appearance of similar reports in the literature, the ability of the astrocytoma to metastasize through the cerebrospinal fluid and to become implanted in remote positions has now become recognized and accepted.

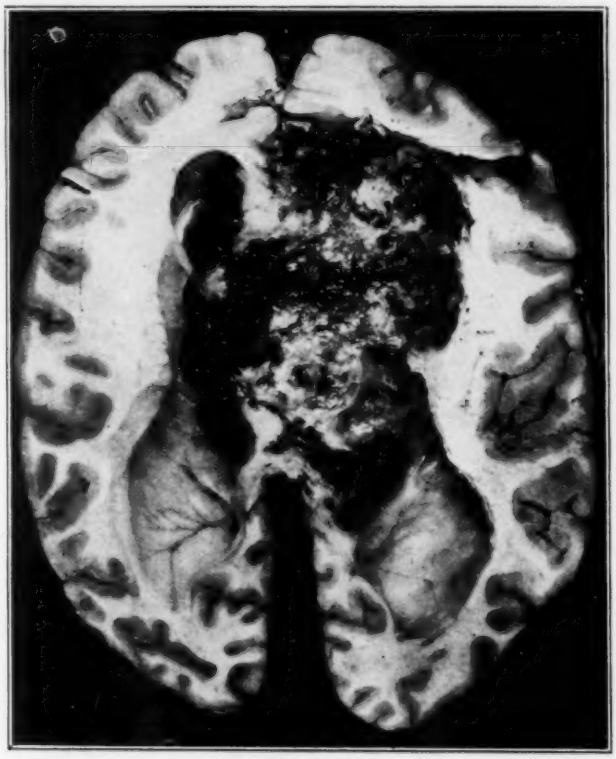

Fig. 6.—Protoplasmic astrocytoma arising from the corpus callosum and extending into the lateral ventricles. The patient lived eight years after the first symptom and seven years after the first operation.

In our series of 42 cases, we found 3 instances in which metastasis from the astrocytoma type of glioma resulted in generalized meningeal gliomatosis (7.1 per cent). In 2 of these cases the tumor was of the protoplasmic type, and in the third it was a fibrillary astrocytoma. The protoplasmic tumors originated in the corpus callosum (fig. 6) and in the third ventricle, respectively, and occurred in patients 15 and 32 years of age. The fibrillary astrocytoma occurred in an 18 year old girl and was primary in the midbrain. In both the cases of protoplasmic astrocytoma, the implantations of tumor were so abundant that the

leptomeninges appeared thickened and opaque (fig. 7 *A*) and resembled those which are seen commonly in the terminal stages of chronic meningitis. Implants also occurred on, and caused adhesions between, the nerve roots of the cauda equina (fig. 7 *B*). The metastatic growths of the fibrillary astrocytoma were not so extensive as those observed with the protoplasmic variety.

Fig. 7.—*A*, implants in the meninges from the protoplasmic astrocytoma seen in figure 6. Note the small nodules and the opacity of membranes. *B*, implants on the nerve roots of the cauda equina, causing adhesions.

The astrocytomas of our series were of the solid type. On gross examination, the borders appeared to be poorly defined, and only a few small cystic cavities were seen. These tumors had the consistency of rubber, and on cross section they were firm, grayish white and homogeneous. The histologic classification of the protoplasmic and fibrillary astrocytomas was dependent on the predominant type of cell.

We employed the phosphotungstic acid hematoxylin stain and the gold chloride–mercury bichloride impregnation method in the identification of these two types of tumors.

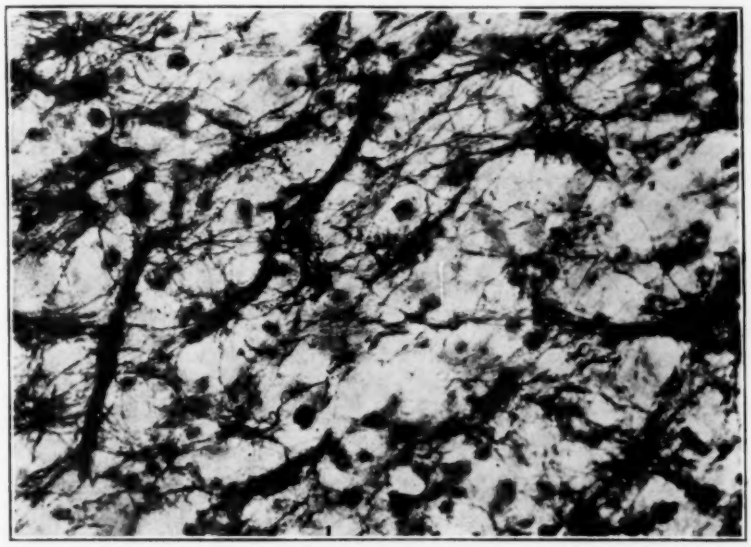

Fig. 8.—Glial process of the tumor cells (protoplasmic astrocytes). Note the abundant capillaries. Cajal's gold chloride–mercury bichloride (sublimate) method; × 240.

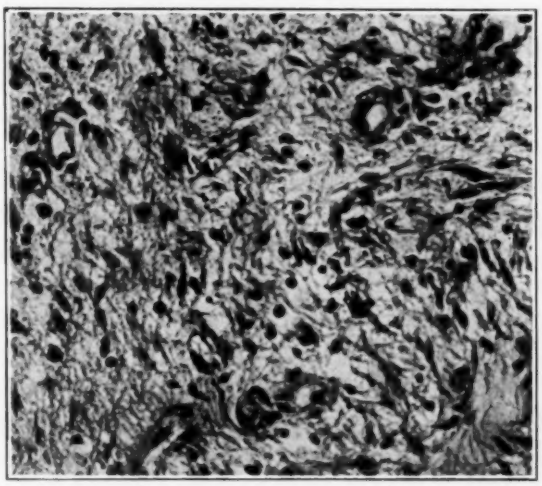

Fig. 9.—Protoplasmic astrocytoma with slight variation in the size and shape of the nuclei. No mitotic figures are visible. Hematoxylin and eosin; × 200.

The matrix of the protoplasmic astrocytomas was coarse and glial processes were common (fig. 8), but glial fibrils were rarely seen. These astrocytomas could possibly be included with the slower-growing

glioblastoma multiforme, since a few multinucleated cells were seen and occasionally amitotic divisions of the nuclei of the cells were encountered. However, mitotic divisions were rarely observed. Vascular changes, such as proliferation of the endothelial cells and adventitia, were noted occasionally in these tumors. In spite of these observations, we consider these 2 tumors as belonging to the class of protoplasmic astrocytoma (fig. 9).

The histologic structure of the fibrillary astrocytoma revealed an abundance of glial fibrils, which formed a dense interlacing network, within which there were scattered nuclei and small blood vessels. The astrocytes and their nuclei were regular in size and distribution, and mitotic figures were rarely seen.

The microscopic appearance of the metastatic implantations from both the protoplasmic and the fibrillary type of astrocytomas was similar to that of the parent tumor. Proliferation of connective tissue was abundant, and there were no regions of degeneration.

RETINOBLASTOMA

Glioma of the retina (retinoblastoma) is a rare neoplasm, often familial, frequently bilateral, and occurs during the period of infancy and early childhood.

We found only 2 cases of such tumors in our series of 42 cases of meningeal gliomatosis (4.8 per cent). The tumors occurred in 4 year old girls, and each originated in the retina of the right eye. In both instances extensive meningeal gliomatosis was present, which involved the leptomeninges of the cerebral hemispheres and the base of the brain. Metastatic nodules of tumor also were observed implanted throughout the ventricular system and around all the cranial nerves.

Gross examination revealed that each tumor was soft and reddish gray and was firmly attached to the surrounding tissue of the brain. In 1 of the cases the tumor infiltrated the left optic nerve so completely that the identification of this structure was difficult, and by this same process the right optic nerve was enlarged to approximately twice its normal size. The metastatic growths from these retinoblastomas were so numerous that the surfaces of the cerebral hemispheres and the cerebellum were almost completely covered by the reddish gray implants.

On histologic examination, the appearance of these tumors was characteristic, with small, dark-staining cells, many typical rosettes and large regions of necrosis. There were numerous mitotic figures.

The metastatic growths from this group of gliomas were as extensive as any of our series. The microscopic structure of the metastatic tissue was identical with that of the parent tumors. Regions of degeneration were prominent features in the implants.

PINEALOMA

Although pinealomas are rare, they constitute a well recognized type of neoplasm. Occasionally the pinealoma forms metastatic growths, which become implanted widely in the leptomeninges of the brain and the spinal cord. We found only 1 instance in our series of 42 cases (2.4 per cent) in which this process occurred. This case has previously been described in detail by Baggenstoss and Love,[15] who in a review of the literature pertaining to this subject found the reports of only 3 similar cases. In another instance, these authors recorded an interesting observation in regard to the metastatic implantation of this tumor. In this case, an infantile type of pinealoma was partially removed in 1937. The patient returned fourteen months later presenting neurologic signs of a lesion of the cauda equina. Lumbar puncture showed a blockage of the circulation of the cerebrospinal fluid. Laminectomy revealed multiple intramedullary and extramedullary tumors of the conus medullaris and cauda equina, the histologic structure of which was identical with that of the original pinealoma.

The pinealoma which we included in our series had extended into, and completely filled, the third ventricle and was implanted throughout the ventricular system. Implants of the tumor also were observed around the roots of most of the cranial nerves and in the leptomeninges of the cerebral hemispheres, the base of the brain, the pons and the medulla. The posterior lobe of the pituitary body was almost completely replaced by the infiltration of these metastatic cells.

Gross examination revealed that the tumor was soft and grayish red and had infiltrated into the surrounding brain. The metastatic implants were numerous throughout the leptomeninges of the brain and spinal cord.

Histologic examination showed that this pinealoma was composed of the typical large parenchymal cells, which were arranged in nests and were separated by columns of connective tissue, infiltrated with clumps of small, round, deeply staining cells, which resembled lymphocytes. Many mitotic figures and giant cells were present.

In histologic structure the implants were identical with the primary tumor, and they had invaded the adjacent portion of the nervous system. There was little connective tissue or capillary proliferation in the metastatic growths. However, regions of degeneration were frequently observed.

FACTORS IN SPREAD OF GLIOMA

Gliomas spread (1) by continuity, (2) by direct extension into the meninges or (3) by their continuous growth; they may reach the ven-

15. Baggenstoss, A. H., and Love, J. G.: Pinealomas, Arch. Neurol. & Psychiat. **41**:1187-1206 (June) 1939.

tricular system or the subarachnoid space and form metastatic growths by spread through the cerebrospinal fluid.

The rate of the production of metastasis through the cerebrospinal fluid was governed by the location of the primary tumor and by its malignancy. Thus, a comparatively slow-growing ependymoma which may originate from the floor of the fourth ventricle can spread more readily and easily through the cerebrospinal fluid of the subarachnoid space than a similar tumor located in the depths of the brain. The rapidity of growth of the tumor became a greater factor in the production of metastasis when the primary tumor originated at a distance from the pathway of the cerebrospinal fluid.

The potential implantation of these tumors which reached the ventricular surface of the brain or the subarachnoid space was influenced by at least four factors: circulation of the cerebrospinal fluid, alterations of the dynamics of the cerebrospinal fluid, gravity and trauma.

The current of the cerebrospinal fluid was partially responsible for the transportation of small particles of tumor to distant sites. Metastatic particles arising from primary gliomas in contact with the cavities of the ventricular system or the subarachnoid space of the brain and spinal cord can enter the cerebrospinal fluid and become widely disseminated throughout the subarachnoid space by the circulating cerebrospinal fluid.

Alteration of the dynamics of the cerebrospinal fluid was probably also a contributing factor in the dissemination of tumor cells through the subarachnoid space. A slight increase of the intraventricular pressure resulting from a partial block of the ventricular fluid could cause the glial cells to become detached from the main mass of the tumor and enter the circulating cerebrospinal fluid, which could carry the particles of tumor to the points where implantation occurred. The dissemination of metastatic tumor may be augmented by a further increase of intracranial pressure, which may be produced when the patient coughs, sneezes, strains or vomits. This process also may be hastened by a decrease of intracranial pressure resulting from the removal of cerebrospinal fluid during lumbar puncture or the course of surgical procedures.

Retrograde metastasis of the tumor against the decreased current of cerebrospinal fluid may have occurred in those instances in which there was internal hydrocephalus. The medulloblastoma group of gliomas was particularly outstanding in this respect. In our series of 20 cases of medulloblastoma, retrograde ventricular metastasis was present in 8 (40 per cent). The mechanism of retrograde metastasis is not clear. However, the intraventricular pressure is probably at first increased, and subsequently decreased, by the patient in coughing, sneezing, strain-

ing or vomiting. Such fluctuations may be important factors in this process. The performance of ventricular punctures for the temporary relief of increased intracranial pressure also may alter the dynamics of the cerebrospinal fluid and produce retrograde metastasis.

Gravity probably influences the implantation of tumor in the subarachnoid space. We found that a common site of early spinal metastasis from primary cerebral gliomas was the pia-arachnoid overlying the dorsal aspect of the thoracic portion of the spinal cord. It is conceivable that the force of gravity plays an important role in the production of metastatic implantation in the pia-arachnoid of this region, since the majority of the patients who have cerebral gliomas are confined to bed and are forced to lie flat on their backs.

Direct trauma as a result of intracranial operation may dislodge the cells of the tumor from the primary mass, and, on entering the circulation of the cerebrospinal fluid, the dislodged cells may become implanted elsewhere. Such an occurrence, perhaps, is most frequent following the surgical treatment of the gliomas of the posterior fossa. This is particularly true of the friable medulloblastomas. .

A sudden increase of intracranial pressure as a result of the patient's coughing, sneezing or vomiting may cause sufficient indirect trauma to dislodge some of the glial cells and produce further metastasis through the cerebrospinal fluid. A sudden jar or a blow on the head may also cause some portions of tumor to be dislodged in the same manner.

Early in the course of meningeal gliomatosis, the metastatic implants and their extensions appeared to be limited to the subarachnoid space. Extensions of the tumors into the adjacent structures of the central nervous system and the subdural space occurred only when the subarachnoid space was completely filled with metastatic tumor at the site of the implantation or when the primary glioma was extremely malignant. We are of the opinion that the restriction of the metastatic tumor to the subarachnoid space is in part at least the result of the normal barriers presented by the leptomeninges. Since there is little or no obstruction to the growth of tumor tissue in the subarachnoid space, extension throughout this cavity is facilitated. Since the vascular pia-arachnoid provides a favorable site for the nourishment and survival of the cells of the tumor, these cells will extend along the surface of this membrane before they will enter the less favorable avascular fibrous arachnoid and the subdural space. However, when metastatic tumors distend the subarachnoid space or when the implants are derived from a malignant variety of glioma, extension into the arachnoid membrane and the central nervous system can be observed.

Although several cases of extracranial metastasis from gliomas have been reported, we found in our series of cases that the metastasis was limited to the central nervous system.

The development of meningeal gliomatosis, therefore, was dependent on a number of factors. The most important factor was access to the pathway of the cerebrospinal fluid, which was determined largely by the location and the malignancy of the primary tumor. The potential implantation of metastatic tumor which reached the surface of the ventricular system or the subarachnoid space was governed by additional factors, such as the circulation of the cerebrospinal fluid, alterations of the dynamics of the cerebrospinal fluid, gravity and trauma. In some instances these factors may occur independently, but more commonly they are in combination.

PATHOLOGIC CHARACTERISTICS

In a review of the pathologic characteristics of the gliomas observed at the Mayo Clinic during the period from 1922 to 1942, inclusive, generalized meningeal gliomatosis was found in 42 instances. We have been unable to confirm the observations of Cairns and Russell in regard to the high frequency of metastasis to the leptomeninges of the spinal cord. However, we are of the opinion that in certain circumstances an extensive involvement of the leptomeninges by metastatic tumor may result from most gliomas.

The metastatic implants which were observed in the walls of the ventricular system and in the pia-arachnoid of the brain and the spinal cord varied greatly in size and distribution. Occasionally these implants were seen as a few small, discrete nodules of tumor in the leptomeninges. At other times, they were microscopic and were found only after a careful histologic study of the entire central nervous system. In other instances, the implants were so numerous that the leptomeninges were opaque and thickened, and occasionally large nodules were visible.

As has been pointed out previously by Cairns and Russell, considerable information may be gained from histologic examination of the metastatic implants if there is doubt as to which type of primary cerebral glioma is involved in the process of meningeal gliomatosis. On several occasions it was necessary to examine the implants histologically before we could classify the cerebral glioma responsible for the metastatic growths. The morphologic character of the cells of the tumor growing on a free surface was different at times from the character of the cells which infiltrated the compact structures of the brain and spinal cord. The histologic structure of the majority of the metastatic implantations, however, was observed to be almost identical with that of the parent tumor. However, the microscopic appearance of the metastatic tissue was frequently somewhat more cellular than that of the primary neoplasm. Occasionally the presence of tumor in the subarachnoid space led to retrograde infiltration of the perivascular spaces of the adjacent

cerebral and spinal structures. The metastatic growths from the more malignant varieties of glioma tended to become invasive and at times almost completely replaced the surrounding structures of the brain and spinal cord, without producing any reaction in these tissues.

GLIAL HETEROTOPIA

The relationship of glial heterotopia to the genesis of a diffuse meningeal gliomatosis should receive consideration. As far as could be ascertained, Wolbach,[16] in 1907, was the first to describe glial heterotopia within the subarachnoid space. These neuroglial nests were observed within the spinal canal of a patient 10 months of age who presented spina bifida with hydrocephalus, as well as a congenital rhabdomyoma of the heart. The nests were most numerous on the dorsal surface of the cervical segment of the spinal cord and were present in the subarachnoid space. At no point were they connected with the spinal cord. These heterotopic glial nests were composed of a dense feltwork of neuroglial fibers, which extended in all directions and were surrounded by a small amount of connective tissue and a few blood vessels, which were derived from the pia mater. The nuclei of the neuroglial fibers were located invariably in the central portion of the tissue and, according to Wolbach, did not differ in any respect from the nuclei of the normal neuroglial tissue in the central nervous system. Two of these neuroglial nests contained ependyma-lined canals, which Wolbach interpreted as further proof of the developmental origin of glial heterotopia.

There have been occasional reports which confirm the observation of Wolbach. In 1931, Kernohan, Woltman and Adson [17] reported 3 instances of gliomas in the subarachnoid space and suggested the possibility of neoplasms originating from such heterotopic masses. In 1936, O. T. Bailey [18] reported a case in which he believed that astrocytoma of the leptomeninges had arisen from a heterotopic neuroglial nest. After the operative procedure, the symptoms progressed, and the patient died thirteen and a half months later. There were neurologic signs of increasing intracranial pressure and bronchopneumonia. Since necropsy was not performed in this case, it is not clear whether the tumor was

16. Wolbach, S. B.: Congenital Rhabdomyoma of the Heart: Report of a Case Associated with Multiple Nests of Neuroglia Tissue in the Meninges of the Spinal Cord, J. M. Research **16**:495-520 (July) 1907.

17. Kernohan, J. W.; Woltman, H. W., and Adson, A. W.: Intramedullary Tumors of the Spinal Cord: A Review of Fifty-One Cases, with an Attempt at Histologic Classification, Arch. Neurol. & Psychiat. **25**:679-699 (April) 1931.

18. Bailey, O. T.: Relation of Glioma of the Leptomeninges to Neuroglial Nests: Report of a Case of Astrocytoma of the Leptomeninges, Arch. Path. **21**:584-600 (May) 1936.

the local extension of a cerebral astrocytoma, a meningeal implantation from a cerebral astrocytoma or an astrocytoma of the leptomeninges which had arisen from a heterotopic neuroglial nest. Bailey, however, mentioned several reasons that he thought the tumor was primary in the leptomeninges:

> The clinical manifestations were referred only to the site at which the tumor was seen. When recurrence developed it was at the same site, and no clinical evidence of tumor elsewhere could be observed. When a glioma metastasizes there is usually seeding in the subarachnoid space, and large solitary nodules do not develop. The gliomas giving rise to a meningeal gliomatosis are confined to the most rapidly growing of the group, especially the medulloblastomas and glioblastomas.[18]

The fact that clinical manifestations of a tumor situated in another portion of the brain were absent in this case would hardly justify Bailey's assumption that the tumor was primary in its location, since it has been well established that tumors in a "silent area" of the brain, especially the frontal lobes, may reach enormous proportions without producing clinical symptoms or neurologic signs. From our observations, meningeal gliomatosis was not restricted to the medulloblastoma and the glioblastoma multiforme group of gliomas. In certain circumstances, this process might occur with almost any type of glioma.

Bailey reviewed the literature pertaining to neuroglial nests and reported 3 cases which he had observed. The heterotopic glial nests in these cases corresponded closely in general distribution and histologic structure to those originally described by Wolbach. They were characterized by being situated entirely in the subarachnoid space, by having a complete, delicate investment of connective tissue and by being composed exclusively of glial cells and fibers except for the presence of a few small vascular channels, which were derived from the vessels of the pia-arachnoid. Nerve cells were absent from the neuroglial nests studied by Bailey.

In 1930, spinal metastasis from a cerebral astrocytoma was reported by Russell and Cairns. The diagnosis in this instance was at first questioned, but in a later report it was confirmed by Cairns and Russell. In commenting on this case, O. T. Bailey stated that he would rather interpret this case as an instance of multiple neuroglial nests with a glioma arising in one of them because of the histologic similarity between the neuroglial nests and the spinal nodules, the location of these nodules in the subarachnoid space, the histologic character of the glioma (astrocytoma) and the absence of similar observations in other instances of this type of tumor. In our study of the astrocytoma group of glioma, generalized meningeal gliomatosis was observed in 3 cases. In 1 of these cases a large protoplasmic astrocytoma was noted in, and incompletely removed

from, the corpus callosum (fig. 6). The patient died seven and a half years later, and implants were seen along the thoracic portion of the spinal cord and on the cauda equina (fig. 7 *A* and *B*). The implants in the meninges of the thoracic portion of the spinal cord and cauda equina were identical histologically with those of the original tumor (figs. 8 and 9). These observations would tend to corroborate those of Russell and Cairns. However, it is possible that both implants from gliomas and those from heterotopic neuroglial nests are the source of neoplastic processes in the meninges.

SUMMARY

In a survey of the glioma group of neoplasms observed at the Mayo Clinic from 1922 to 1942, inclusive, generalized meningeal gliomatosis was found in 42 instances. The medulloblastoma was responsible for generalized metastasis in 47.6 per cent of the cases. Glioblastoma multiforme represented 14.3 per cent of the series, and the order in which the other types of tumors occurred is as follows: ependymoma and ependymoblastoma, 11.9 per cent; oligodendroglioma and oligodendroblastoma, 11.9 per cent; astrocytoma, 7.1 per cent; retinoblastoma, 4.8 per cent, and pinealoma, 2.4 per cent.

Although several instances of extracranial metastasis from gliomas have been reported, we found in our series that the metastatic implants were limited entirely to the central nervous system. Furthermore, the metastatic growths were more or less confined to the subarachnoid space because of the normal barriers formed by the anatomic features of the leptomeninges of the brain and spinal cord. The pia mater and the subarachnoid space, being extremely vascular, furnish a suitable environment for the nutrition and the survival of the cells of the tumor. The extension of the cells is limited peripherally by the fibrous, inelastic and avascular dura mater and arachnoid membrane and centrally by the compact structures of the brain and spinal cord.

The microscopic appearance of the metastatic implants was similar to that of the primary tumor except in 1 instance, in which the subarachnoid extension from an intramedullary cellular ependymoma of the spinal cord assumed the microscopic characteristics of a well differentiated oligodendroglioma. In the majority of the cases the cells of the metastatic tissue were easier to identify than those of the primary tumors, probably because they grew on a free surface and the morphologic characteristics of these cells were unaltered by the pressure of the adjacent cerebral and spinal structures.

The metastatic growths of the tumors exhibited several interesting histologic features. Occasionally the presence of metastatic tumor in the subarachnoid space produced a moderate amount of lymphocytic reaction within the adjacent cerebral and spinal tissues. At times the

leptomeninges produced a proliferation of connective tissue in response to the implantation of metastatic tumor. This was seen most frequently in association with the slow-growing gliomas, such as the astrocytoma and the oligodendroglioma. Capillary proliferation and focal degeneration were observed to be most prominent in the implants from the rapidly growing gliomas.

Contrary to the general belief that only the more malignant varieties of glioma produce generalized meningeal gliomatosis, we found that in certain circumstances this process may result from almost any variety of glioma.

The Mayo Clinic.

EDUCABILITY OF A "DETERIORATED" EPILEPTIC PATIENT

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CINCINNATI

STATEMENT OF PROBLEM

IN THE literature on epilepsy, reference is commonly made to the deteriorated epileptic patient [1] and to progressive deterioration. It is proposed in this paper to raise the question whether there is evidence to justify a continuation of the implication in the literature that there is a special type, or greater degree, or higher incidence, of deterioration in epilepsy than in other diseases, and whether there is justification for the implication that the fits per se lead, or even largely contribute, to deterioration. The following case of a "deteriorated" epileptic patient is presented as the basis for raising such questions.

REPORT OF CASE [2]

Family Data.—The mother and father, born in Ohio, were of German and Swiss extraction, respectively. The father, a business man, kept his family comfortably, but an unfortunate business venture shortly before his death left his family in straitened circumstances. The children proved themselves to be enterprising and capable. Six earned their way for two or more years at the state university.

No case of epilepsy was found in this family, including the siblings of the parents' families and their children. The electroencephalographic tracings [3] made for the mother and 8 of the patient's siblings showed no abnormalities, with or without hyperventilation.

Clinical History.—According to the mother, the patient's first attack occurred on Good Friday, 1923, when he was 6 years old. He was the tenth of 11 children. Labor, birth and developmental history were normal. He escaped the usual dis-

1. (*a*) Wechsler, I. S.: Textbook of Clinical Neurology, with an Introduction to the History of Neurology, ed. 5, Philadelphia, W. B. Saunders Company, 1943, p. 641. (*b*) Strecker, E. A., and Ebaugh, F. G.: Practical Clinical Psychiatry, ed. 5, Philadelphia, The Blakiston Company, 1940, p. 187. (*c*) Ford, F. R.: Diseases of the Nervous System in Infancy, Childhood and Adolescence, ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1944, p. 1080.

2. The material from the physical examination and the clinical and family histories has been taken largely from a paper by H. D. Fabing and D. Twitchell-Allen (The Case of Eugene Z.: A Preliminary Report, read before the Section on Convulsive Disorders of the American Psychiatric Association, Cincinnati, May 20, 1940).

3. All encephalographic tracings reported in this paper were made and interpreted by Dr. Douglas Goldman, Director, Medical Department, Longview State Hospital, Cincinnati.

eases of childhood. Of possible etiologic significance was a fall down the cellar stairs at the age of 4 years, which rendered him unconscious for several minutes. The family and the priest and nuns of the one school he attended remember that before the onset of seizures he was alert and apparently above average in ability. His seizures varied in frequency from one a week to as many as eighteen grand mal fits in one day. Aura, in the form of abdominal pains, usually preceded the severe spells. A variation of the grand mal attack was the epileptic fugue, in which the patient after the aura and tonic-clonic fit would rouse from the coma and, in a state of confusion, rush out of the house and walk rapidly around the block. At such times he would fight with any one who tried to stop him.

This seventeen year period represents a block of the patient's life, from his sixth to his twenty-third year, which was spent in practical isolation. He tried to complete his first year of school, and in the fall to enter second grade, but he was sent home both times because of frequent spells. In his yard, where many children gathered to play with his siblings, he became more and more an outsider. At the age of 14 he became unmanageable and was placed in the Gallipolis State Hospital, where he remained eighteen months. After returning home, he withdrew increasingly from family activities. The stupor from the fits themselves or from the continuous use of phenobarbital became more and more his characteristic state.

Physical Examination.[2]—The patient was admitted to the hospital on Nov. 8, 1939. He was having a shower of minor seizures, which were accompanied by a fixed, vacant stare or spontaneous giggling or by the head rolling and the eyes closing. General physical and neurologic examinations, a study of the cerebrospinal fluid and roentgenologic studies of the skull gave normal results. Later, an air encephalogram[4] was concluded to show moderate cortical atrophy. Electroencephalograms, taken at later dates, showed pronounced irregularity in all leads, with little alpha rhythm and predominance of low and high voltage slow waves, of 3 to 7 per second. Subsequent study showed that the patient had a basal metabolic rate of + 15 per cent. A five hour dextrose tolerance curve had a normal configuration, with a fasting level of 94 mg. per hundred cubic centimeters.

When he arrived at the hospital, the patient was taking three doses of elixir of phenobarbital daily, 4 cc. to the dose; he was kept on this medication until November 15. On November 8 he was also placed under treatment with sodium diphenylhydantoin, 1½ grains (0.1 Gm.) three times a day. For one week the patient was taking both phenobarbital and diphenylhydantoin sodium; thereafter he was maintained on the latter alone. Seizures stopped at once with the administration of diphenylhydantoin and have not recurred during the continuation of this medication.

Psychologic Study.—On Nov. 29, 1939 the patient came to me for special study. He shuffled along, with shoulders stooped and head forward, his arms immobile at his sides. The expression on his face was that of a mask. His speech was mumbling. If traditional statements regarding epileptic deterioration had been accepted uncritically, the patient would have been termed deteriorated, particularly since on that day, at the age of 23, the patient obtained a mental age of 6 years and 7 months on the Stanford-Binet Form L Test.

When, during the neurologic study, the patient's medication was changed from phenobarbital to diphenylhydantoin sodium attacks ceased immediately, and the patient suddenly was thrown into a position where he might enter society and

4. This encephalographic study was made by Dr. Joseph P. Evans, of the University of Cincinnati College of Medicine.

5. Footnote deleted by the author.

participate in normal group living. But how much could he learn at the age of 23, after seventeen years of a minimum of thinking, wracked by an estimated minimum of 2,200 grand mal and an untold number of petit mal attacks?

In accordance with the purpose of this investigation, a program was set up to foster continuous progress in mental, social and emotional development. From my first tests to the last test here reported, this program consisted of nine periods. The first was a two month period in the patient's home following the institution of medication with diphenylhydantoin sodium. During this time the patient was encouraged to learn certain habits of self care. For example, one of his brothers taught him to shave himself.

The second period was in my home, where the patient remained for four months as a member of my family. During this time he was tutored two and a half hours daily five days a week by an experienced elementary school teacher. In addition, certain activities were directed toward personality growth, such as trips to the zoo. Some activities emphasized interpersonal relationships, such as having school boys as guests for dinner.

The third period was six months at the Devereux school and camp. This afforded opportunity for the patient to progress in ways in which his development lagged as long as he remained in a family situation. It was thought that the attractiveness of camp activities could enhance the motivation to learn skills and to get along with his peers.

The fourth period was a month in the home of the neurologist, while I was testing him and while plans were being made for another period of individual tutoring.

The fifth period was four months of daily tutoring by an experienced high school teacher, who at the time was a graduate student [6] at the University of Cincinnati Teachers College. The patient had to live in a city of 500,000 in a boarding home. Daily he had to walk a mile (1.6 kilometers) to the university, crossing streets of heavy traffic. He started weekly lessons in piano, swimming and reading [7] and biweekly lessons in speech. He ate daily at the student cafeteria, usually with his tutor and other graduate students, whom he heard discuss instructors, assignments, examinations and grades.

The sixth period was four months in his own home. The family was asked to accept him as a normal person and to help him obtain a job. He did attempt two small jobs but was unsuccessful.

The seventh part of the guidance program was a tutoring period of a complete academic year. For vacations he traveled alone the 100 miles (160 kilometers) to his home by train. The program of instruction was similar to that of the previous term except that classes in religious education and art were added. The second semester he entered the Cincinnati Art Academy and worked five mornings a week.[8] Social contacts with the men and women of the class were one advantage of this course. Paralleling this experience were reading lessons, in which he studied the social concepts found in "Young Citizens in a Democracy: Growing Up" [9] for third and fourth grade pupils.

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6. Munger, I. L.: A Case Study of Delayed Intellectual and Social Development, Teachers College, University of Cincinnati, 1944, unpublished thesis.

7. With the late Miss Frances Jenkins, assistant professor in the University of Cincinnati Teachers College.

8. Under Mr. Willson Y. Stamper, formerly of the Cincinnati Art Academy, now director of the Honolulu School of Art.

9. Jenkins, F., and Campbell, J. T.: Young Citizens in a Democracy: Growing Up, Columbus, Ohio, American Education Press, Inc., 1941.

The eighth period was an unsuccessful attempt to place the patient in a position where he could learn skills useful for earning a living. He was placed on a farm, where he remained only one month.

The ninth period was with his family. He obtained a job as yard man for a neighbor for six hours a day five days a week. During the war period he received more requests to work than he could accept.

Diphenylhydantoin sodium has been used as the anticonvulsant since November 1939. The original dose of 0.3 Gm. daily seemed inadequate, since he was too lethargic for his studies. With 0.4 Gm. the patient could concentrate better. Both 0.5 and 0.6 Gm. daily were tried, and 0.5 Gm. daily was found to be optimal. He received this dose until November 1941, at which time he was placed on a regimen of 0.4 Gm. daily because of slight signs of toxicity. In September 1944 the patient himself decided to reduce the dosage to 0.3 Gm. daily.

Results: The patient's development in terms of his mental age was measured periodically by four standardized tests for intelligence. All four tests, the Stanford-Binet Form L,[10] the Stanford-Binet Form M,[10] the Arthur Performance Form I [11] and the Wechsler-Bellevue [12] test, showed an increase in the mental age. The mental age in November 1939 was 6 years 7 months (Stanford-Binet, form L); in June 1944 it was 13 years 2 months (Wechsler-Bellevue). It was seen that the patient's mental age increased at a rate equal to or faster than that of a child of average intelligence and the chronologic age of 6 years 7 months.

On the Wechsler-Bellevue test the ratio of deterioration [12] for each of the three test results over a two year period was 3 per cent or less, and thus noncritical (11 to 20 per cent is "possible deterioration"; above 20 per cent is "definite deterioration"). Failure to find evidence of deterioration in epileptic persons has been reported.[14]

The patient learned to follow a day's schedule, to speak with normal enunciation, to swim the crawl stroke and to play simple arrangements of folk songs and classics on the piano. He progressed from preprimer to fourth grade reading.[14a] His drawing evinced a widened range of thought and loosening of his rigid personality. He obtained and has held a job, earned wage raises, been offered new jobs and bought war bonds.

COMMENT

What is the significance of these results in terms of the concept of epileptic deterioration? This discussion will be limited to idiopathic epilepsy. In the literature such a differentiation has not always been made.

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10. Terman, L. M., and Merrill, M. A.: Measuring Intelligence: A Guide to the Administration of the New Revised Stanford-Binet Tests of Intelligence, New York, Houghton Mifflin Company, 1937.

11. Arthur, G.: A Point of Performance Tests, ed. 2, New York, The Commonwealth Fund, 1943.

12. Wechsler, D.: The Measurement of Adult Intelligence ed. 3, Baltimore, Williams & Wilkins Company, 1944.

13. Footnote deleted by the author.

14. Falk, R.; Penrose, L. S., and Clark, E. A.: The Search for Intellectual Deterioration Among Epileptic Patients, Am. J. Ment. Deficiency **49**:469-471 (April) 1945.

14a. Jenkins, F., and Students: Jenkins Oral Reading Test, Forms A and B, Cincinnati, C. A. Gregory Company. Gray, W. S.: Gray Oral Reading Paragraphs Test, Bloomington, Ill., Public School Publishing Company.

Authors frequently refer to deterioration as the result of seizures,[15] the progression allegedly being dependent on the frequency of the convulsions. The case here discussed does not substantiate such statements and calls for a redefinition of "deterioration."

Lowered mental functioning may result from prolonged sedation.[16] In the case of this patient, certain improvements occurred immediately after treatment with phenobarbital was discontinued and diphenylhydantoin therapy begun. However, extensive improvement in personality occurred only after close regulation of diphenylhydantoin therapy and a special guidance and tutoring program had been instituted. Experience in this case, and in others reported by Harrower-Erickson,[17] indicates that generalizations regarding permanent change in personality based on sedation are not warranted.

This case supports the theory proposed by Putnam and Merritt[18] that intermittent "dulness" may be one symptom of a pathologic condition of the brain, of which the convulsions themselves are but another aspect. Although control with diphenylhydantoin sodium did not eliminate all fluctuation in this case, careful regulation of the intake of the drug beyond that necessary for cessation of seizures reduced the degree of variability from day to day.

It must be emphasized that in this case an educational program was requisite for reinstatement of any degree of normalcy and that as the patient's needs matured the program had to be changed to afford opportunities for continued growth.

SUMMARY

The case is reported of a white man aged 23 who had had idiopathic epilepsy for seventeen years, with almost continuous grand mal and petit mal seizures, and who at the end of this time appeared to be rather completely deteriorated. Remarkable strides toward normalcy appeared to be the result of removal of phenobarbital medication and close regulation of seizures with diphenylhydantoin sodium, and a psychologic guidance program over a four and a half year period.

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15. Graves, R. W., cited by Davison, W. C.: The Compleat Pediatrician: Diagnostic, Therapeutic and Preventive Pediatrics, ed. 4, Durham, N. C., Duke University Press, 1943, par. 97. Kanner, L.: Child Psychiatry, Springfield, Ill., Charles C Thomas, Publisher, 1935, pp. 176 and 423. Collins, L. A.: Psychometric Records of Institutionalized Epileptics, J. Psychol. **11**:359-370 (April) 1941. Ford.[1c] Wechsler.[1a]

16. Penfield, W., and Erickson, T. C.: Epilepsy and Cerebral Localization: A Study of the Mechanism, Treatment and Prevention of Epileptic Seizures, Springfield, Ill., Charles C Thomas, Publisher, 1941, pp. 553 and 554.

17. Harrower-Erickson, M. R.: Psychological Studies of Patients with Epileptic Seizures, in Penfield and Erickson,[16] pp. 546-574.

18. Putnam, T. J., and Merritt, H. H.: Dulness as an Epileptic Equivalent, Arch. Neurol. & Psychiat. **45**:797-813 (May) 1941.

The case appears significant in pointing to the need for clarification of the concept of epileptic deterioration. To this end, it seems important to treat cases of idiopathic epilepsy separately from those of other convulsive disorders in statistical or clinical studies, to use discrimination in applying the concept of the deteriorative results of the seizures themselves, to differentiate the effects of sedatives and intermittent dulness from chronic impairment and to separate those forms of inferior functioning which represent emotional reaction to disease from those derived from neurosomatic deterioration.

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Case Reports

CONCUSSION OF THE SPINAL CORD

Report of a Case with Radiculoneuritic Manifestations

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THAT a transient abrogation of the functions of the spinal cord may follow direct or indirect trauma to the vertebral column has long been a clinically recognized phenomenon. The pathologic and pathophysiologic basis of concussion of the spinal cord has been the subject of much controversy and is still far from being definitely determined. Part of the confusion surrounding the subject has been due to a disagreement as to whether cases with demonstrable pathologic changes should be included with those of concussion of the spinal cord. Although most authors feel that they should, others (Marburg,[1] Cavichia and Rosa[2]) maintain that in true concussion of the spinal cord observable changes are reversible or do not occur. Since the syndrome is characterized by evidence of neurologic damage at levels distant from the site of the original trauma, a comprehensive theory of the condition should consider a mechanism of diffusion or dispersal of the lesions, and this has been a further source of difficulty.

On the basis of animal experimentation, Schmauss and Docki[3] expressed the belief that the force applied to the vertebral column was transmitted through the cerebrospinal fluid to the spinal cord and its blood vessels, producing hemorrhages and tears of the parenchyma. That such changes actually occur has been demonstrated experimentally in rabbits by Ferraro[4] and in human autopsy material by Davison.[5] According to Henneberg,[6] after concussion a vascular stasis occurs, with resulting degeneration and necrosis of the nerve tissue. Erichsen[7] advanced the idea of "molecular" disturbances of the cord as a

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1. Marburg, O.: Rückenmark und Gehirn: I. Die traumatischen Erkrankungen des Rückenmarks, in Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1936, vol. 11, p. 101.

2. Cavichia and Rosa, cited by Ferraro.[4]

3. Schmauss, H., and Docki, S.: Vorlesungen über die pathologische Anatomie des Rückenmarks, Wiesbaden, J. F. Bergmann, 1901.

4. Ferraro, A.: Experimental Medullary Concussion of the Spinal Cord in Rabbits: Histologic Study of Early Stages, Arch. Neurol. & Psychiat. **18**:357-373 (Sept.) 1927.

5. Davison, C.: Pathology of the Spinal Cord as a Result of Trauma, A. Research Nerv. & Ment. Dis., Proc. (1943) **24**:151-187, 1945.

6. Henneberg, R.: Erweichung des Sakralmarkes nach Schuss in die Brustwirbelsäule, Berl. klin. Wchnschr. **52**:859, 1915.

7. Erichsen, J. E.: On Concussion of the Spine, New York, Wm. Wood & Co., 1875.

result of physical impact directly on the vertebrae or of a general shaking or jarring of the body, as when one is riding in a railroad carriage. According to Elsberg,[8] in persons who recover from damage to the cord within twenty-four to forty-eight hours the lesion responsible is probably edema. Although the results of modern experimental research on the mechanism of cerebral concussion have not as yet been applied to the spinal variety of concussion, there appears to be no reason that the observations of Denny-Brown and Russell [9] on the effect of sudden acceleration in producing a direct traumatic paralysis of nervous function cannot be true of the spinal cord as well as of the brain. The experiments of Walker and associates,[10] in which the effects of cerebral concussion were explained as the result of a direct traumatic depolarization of many neurons with immediate discharge of axons, followed by after-discharge and then by cortical extinction, offer fruitful possibilities of application to the phenomena of concussion of the spinal cord. This would provide a physiologic basis for some cases of concussion of the spinal cord in which the neurologic abnormalities are of brief duration.

The part played by lesions of the nerve roots and peripheral nerves in cases of concussion of the spinal cord has been recognized in some reports but has not been particularly emphasized. Lhermitte [11] stated that radicular changes had been observed in several cases of concussion of the spinal cord but presented no pathologic material of his own. Hassin [12] reported a case in which microscopic lesions of the cauda equina were seen after fracture of the lumbar vertebrae, although there had been no contact between the fractured bone and the damaged nerve tissue. In Davison's [5] material the nerve roots displayed swelling of the epineurium and perineurium and swelling and disintegration of their myelin sheaths and axis-cylinders. Elsberg [8] stated the belief that in most cases of trauma to the cord there is an associated lesion of the spinal nerve roots and that occasionally the roots are involved without any evidence of damage to the cord. In the rabbits subjected to experimental concussion by Feraro,[4] lesions of the nerve roots, particularly the posterior roots, were observed and were attributed to the combined result of the action of the cerebrospinal fluid set in motion by the shock of the injury and the displacement of the spinal cord, producing traction on the relatively fixed roots.

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8. Elsberg, C. A.: Surgical Diseases of the Spinal Cord, New York, Paul B. Hoeber, Inc., 1941.

9. Denny-Brown, D., and Russell, W. R.: Experimental Cerebral Concussion, Brain **64**:93-153 (Sept.) 1941.

10. Walker, A. E.; Kollros, J. J., and Case, T. J.: Physiological Basis of Concussion, J. Neurosurg. **1**:103-116 (March) 1944.

11. Lhermitte, J.: La section totale de la moelle épinière, Bourges, Imprimerie V. Tardy, 1919.

12. Hassin, G. B.: Pathological Considerations of Contusion of Cauda Equina, A. Research Nerv. & Ment. Dis., Proc. (1943) **24**:188-200, 1945.

Scheinker [13] reviewed the literature on the condition of the peripheral nerves and the spinal nerve roots in cases of concussion of the spinal cord and failed to find a single study prior to the publication of his paper in which histologic changes were reported. In his case, clinical signs of involvement of the spinal nerve roots and the peripheral nerves developed two or three days after an injury to the back in a man aged 51, whose health had previously been good. Death occurred two and one-half months after the injury, and autopsy revealed extensive pathologic changes, consisting of swelling, degeneration and demyelination of the nerve roots and of the peripheral nerves.

In the following case, a typical clinical syndrome of concussion of the spinal cord was associated with certain features strongly suggesting that lesions of the spinal nerve roots and peripheral nerves played a considerable role in producing the total picture.

REPORT OF CASE

A 29 year old sergeant was admitted to the station hospital, Langley Field, Va., on Nov. 21, 1945. Shortly before admission, he had been standing on an outside platform about 4 feet (120 cm.) above the pavement, when his heel caught in the edge of the platform and he had fallen face forward, to the ground. While falling, he had violently thrown his head and shoulders back in an effort to maintain his balance, and this, together with the fact that his heel was caught on the edge, resulted in a marked hyperextension of his back. At the same time he was thrusting his arms and hands forward in an attempt to break the fall. This was only partially successful, and he struck his chin and nose heavily enough to cause bruising and nosebleed. He was immediately conscious of a tingling pain involving the upper extremities and, to a less extent, the entire body below the chest and the lower extremities. He was unable to move his legs or body and for a few minutes could not move his arms. The ability to move his arms returned quickly, but by the time he was first seen in the hospital there was still almost complete paralysis of the lower extremities. At this time there was a sensory level at about the nipple line, below which there was pronounced diminution of all modalities of sensation. The deep reflexes were generally equal and active, and there were no pathologic reflexes.

Within about two hours, the sensory level gradually and steadily fell and the power of movement began to return to the lower extremities. When the return of sensation reached the thighs and legs, it was noted that the area of retreating residual sensory loss assumed a pattern like that of a peripheral polyneuropathy, rather than a segmental distribution. That is, the area of diminished sensation involved both legs in a steadily decreasing stocking distribution. Because of their extreme sensitivity and the continued presence of spontaneous tingling pain, the upper extremities could not be accurately examined.

By the next day, sensation had almost entirely returned to the legs and there was considerable return of motor power to them. In the next week there were complete return of power to the lower extremities and complete return of sensation. The improvement in the upper extremities, however, was much slower and more incomplete. By November 30, the pain and tingling were largely confined

13. Scheinker, I. M.: Post-Traumatic (Concussion) Changes in the Spinal Cord, Roots and the Peripheral Nerves, J. Neuropath. & Exper. Neurol. **1**:181-187 (April) 1942.

to the portions of the hands and forearms supplied by the ulnar nerve, and there were weakness and sensory diminution in these areas. On December 12, examination revealed no neurologic abnormalities of the lower extremities. Both hands were somewhat mottled, and there was an increase in palmar sweating on both sides. The hands, especially the portions supplied by the ulnar nerve, were hypersensitive to cold and heat and to sudden pressure. The ulnar nerves at the olecranon fossae were insensitive even to strong pressure. There was weakness of flexion movements of the ring and little fingers bilaterally, and the patient could not entirely close his fists. The other fingers were moved freely in all directions, without weakness. There were hypalgesia, hypesthesia and hypothermesthesia over the ring and little fingers, the ulnar portions of the hands and the forearms up to about the elbows. The involvement was about equal on the two sides and corresponded to the eighth cervical and first thoracic dermatomes. There was considerable but incomplete improvement in the next month, so that by January 11 the spontaneous pain was much less severe, there was only slight weakness of flexion of the fingers supplied by the ulnar nerve and the areas of sensory diminution, still equal on the two sides, included only the ring and little fingers and the ulnar portion of the hand as far as the wrist. The patient had no other complaints and was anxious to return to duty.

When he was first seen, there was considerable pain in the dorsal region of the spine. This later became localized at the fourth dorsal vertebra, which remained tender for three weeks. Roentgenograms of the dorsal portion of the spine, including spot films of the fourth dorsal vertebra, taken immediately after the accident and checked later, showed no evidence of osseous damage or displacement. A spinal puncture was not performed until Jan. 15, 1946. At that time the manometric and laboratory findings were within normal limits.

COMMENT

The sequence of events in this case, the sudden indirect trauma without evidence of injury or discoloration of the bony spine, followed immediately by evidence of widespread subcranial neural dysfunction and within a short time thereafter by notable improvement, is compatible with that seen in cases of concussion of the spinal cord. The fact that recovery was not complete and that there were more or less permanent residual symptoms does not at all invalidate the diagnosis, since persistence of symptoms of varying grades of severity frequently occurs. Syndromes simulating amyotrophic lateral sclerosis resulting from concussion of the spinal cord have been reported (Hassin [14]).

Analysis of certain features of the case, however, casts doubt on the presumption that the entire picture resulted from purely intramedullary damage to the cord and suggests that radiculoneuritic involvement was also present and played a major role.

Since the accident occurred at a very short distance from the hospital, the patient was seen less than a half-hour after the injury, and the rapidly subsiding sensory impairment could be followed almost from the beginning. As noted in the case report, this was observed to assume a pattern

14. Hassin, G. B.: Concussion of the Spinal Cord: A Case with the Clinical Picture of Amyotrophic Lateral Sclerosis, Arch. Neurol. & Psychiat. **10**:194-211 (Aug.) 1923; Traumatic Degeneration of the Spinal Cord (Spinal Concussion), J. Neuropath. & Exper. Neurol. **1**:100-110 (Jan.) 1942.

suggestive of widespread but not profound damage to the peripheral nerves, rather than the segmental distribution which would be expected in the case of recovery from an acute insult to the spinal cord itself. In the upper extremities the neuritic pattern was not so apparent, possibly because the extreme hyperalgesia made examination difficult, but more probably because the picture was here complicated by involvement of the lowest cervical and upper dorsal nerve roots, as could be clearly seen later after the early symptoms had disappeared. Examinations subsequent to the first two weeks revealed bilateral sensory loss in the areas of the eighth cervical and first thoracic dermatomes, indicating that the corresponding nerve roots had been damaged by the initial trauma. The tingling "pins and needles" type of pain complained of by the patient was also suggestive of a sudden stretching or percussion of peripheral nerves and nerve roots rather than of an intramedullary lesion, in which case a burning, poorly defined and localized pain would have been more likely. It is of interest that the patient voluntarily described his pain as resembling that which occurs when the "crazy bone" is struck. However, the insensitivity of the ulnar nerves at the olecranon fossae indicated lesions higher up, and the area of sensory loss of the upper extremities was too extensive to be accounted for by ulnar neuropathy alone.

The fact that all modalities of sensation were implicated in both the original and the residual areas of sensory loss, while not ruling out involvement of the entire cord, is more easily explained on the basis of peripheral and radicular lesions. This absence of sensory dissociation is an especially cogent argument in favor of root rather than intramedullary origin for the persistent changes in the upper extremities.

It is thus seen that the type of sensory pattern observed both immediately and later, the kind of pain felt by the patient, the lack of sensory dissociation and the residual root syndrome are strongly suggestive of a predominant radiculoneuritic origin of the symptoms and signs in this case of so-called concussion of the spinal cord. A further analysis of the mechanics of the trauma indicates how this state of affairs could have been brought about. When the patient fell from the platform, with his heels caught on the edge, his efforts to break his fall caused him to throw his hands and arms as far forward as possible, while his shoulders were forcibly drawn back by his attempt to preserve his balance and keep himself from falling. With his heels fixed, there was a pronounced arching of his back during the fall. This combination of movements and countermovements produced a relative lengthening of all limbs with a consequent general, sudden and brief stretching of the peripheral nerves, while at the same time the maximum possible amount of movement of the spinal cord and attached nerve roots occurred with relation to the fixed spine. It is quite likely that in this process the nerve roots were sufficiently agitated within the intervertebral foramens to cause them to be struck against the containing bony walls. Since the greatest stress occurred at the level of the fourth thoracic vertebra, it is logical to expect the greatest damage to the roots at or near this level, and this actually occurred, since the eighth cervical and first thoracic roots, the sites of the principal damage, were the closest large roots to the vertebral level mentioned. It is also pertinent, as Elsberg [8] has mentioned, that force applied in the direction of the axis of the vertebral column is more likely

to damage cervical roots, as occurred here, while force applied transversely will result in injury to the lumbar and sacral roots.

That physical impact can produce a transient abrogation of neural functions has long been recognized and has been studied experimentally by Denny-Brown and Brenner,[15] who found that percussion of a nerve will produce with regularity a pseudoneuroma associated with either transient or more permanent paralysis, depending on the intensity of the process. Denny-Brown and Doherty [16] showed that stretch of nerves can similarly produce all gradations between simple pseudoneuroma and spindle neuroma, with resultant temporary or lasting interference with conductivity. Krems, Schoepfle and Erlanger [17] showed that nerves subjected experimentally to sudden compression develop a conduction block distad to the point of application of the compressing force.

If this combination of stretching and concussion of the peripheral nerves and compression of nerve roots can be shown to occur in other cases falling within the limits of concussion of the spinal cord, an adequate and rational explanation for the occurrence of manifestations of neurologic disorder at a distance from the site of the original injury is available, as an alternative to the necessity of postulating the presence of widespread parenchymal tears in every case. In view of the variety of pictures subsumed under the term concussion of the spinal cord and the numerous ways in which they can be caused, it appears possible that closer attention to the peripheral nerves and spinal roots may provide explanations for some of the puzzling features of these cases.

SUMMARY AND CONCLUSIONS

In the case reported, a clinical picture compatible with concussion of the spinal cord appeared after an injury to the dorsal portion of the spine, but on analysis was found to be associated with certain features suggestive of a radiculoneuritic origin of the symptoms and signs.

Stretching of the peripheral nerves and traction and compression of the nerve roots in the intervertebral foramens at the time of the injury are believed to provide the basis for the disturbance in function of the nerves and nerve roots.

In cases of concussion of the spinal cord, radiculoneuritic involvement may explain the occurrence of certain puzzling features and may serve as an alternative explanation to that of widespread parenchymal tears in accounting for signs of neural damage at a distance from the original site of the injury.

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AN ELECTROENCEPHALOGRAPHIC STUDY OF HELEN KELLER

WILLIAM C. STILL, NEW ORLEANS

ALMOST every one is familiar with the case of Helen Keller and her remarkable mastery of the handicap she suffered so early in life. Hers was a normal life until the age of 19 months, when she had a severe illness, of sudden onset and short duration, which left her totally blind and deaf.

Berger [1] and Loomis, Harvey and Hobart [2] reported the presence of alpha rhythm in blind persons. Gibbs and Gibbs [3] reviewed the literature and studied the effects of auditory, visual and tactile stimuli on the occurrence and amplitude of alpha waves. Visual and auditory stimuli are automatically ruled out in the case of Helen Keller because of her total blindness and deafness, and tactile stimuli, to have any effect on the alpha waves, must attract the subject's attention. Hence, tactile stimulation was the only external stimulation it was necessary to control in this study.

Adrian and Matthews [4] and Jasper and Andrews [5] showed that the occipital areas in children and in adults usually have more alpha activity, and the frontal and parietal areas more 15 to 30 cycles per second activity, than any other area.

According to Gibbs and Gibbs,[6] there are relatively few cases in which the alpha activity, although present in all leads, has a higher amplitude in the frontal and motor (parietal) leads.

These facts are significant in a critical analysis of the electroencephalogram of Helen Keller, who was 64 years of age at the time of this examination.

From the Department of Electroencephalography, LaGarde General Hospital.

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METHOD

The electrical activity from four cortical areas was recorded simultaneously with a four channel Grass electroencephalograph. Monopolar leads were used for routine examination, according to Gibbs's standard technic.[7]

Recording was done under standard conditions, namely, in a darkened and electrically shielded room, which was air conditioned. (Warmer climates necessitate air conditioning as an integral part of laboratory facilities if reliable results are to be obtained.) For the patient's comfort, an examining table with an air mattress was substituted for the usual easy chair. In prolonged examinations, the examining table or bed is much preferred, since fatigue is minimized and artefacts due to muscular tension and movement are substantially reduced.

Analysis of this record is primarily in terms of variation in amplitude and of the alpha index. The alpha index is the percentage, that is, the number of centimeters, of alpha activity (at least three consecutive waves of 8.5 to 12.0 cycles

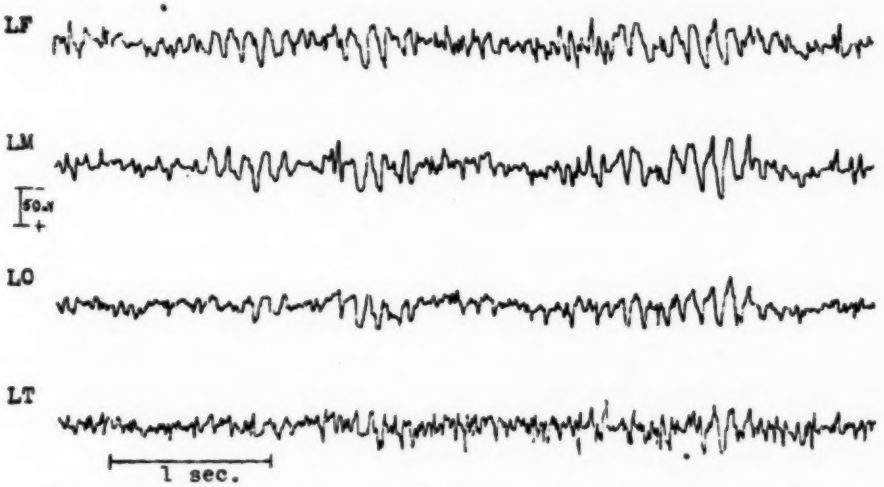

Fig. 1.—Increased amplitude of alpha waves in frontal and motor leads during the resting stage.

per second) in a continuous sample of record 1 meter in length. Alpha indexes were computed for the resting phase of the electroencephalogram and for varying intervals after three minutes of hyperventilation. Amplitude averages for the frontal, motor and occipital areas were computed by measuring each of a representative series of the alpha waves found in the resting stage and in the post-hyperventilation stages. The samples used for measurement of amplitude were the same as those used in determining the alpha indexes.

Since all patients do not cooperate to the same degree in hyperventilation, it has been found desirable in certain instances to allow a longer period for hyperventilation than that adopted by Gibbs and associates.[8]

7. Gibbs and Gibbs,[3] p. 22.

8. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: Electroencephalographic Response to Overventilation and Its Relation to Age, J. Pediat. **23**:497-505 (Nov.) 1943.

OBSERVATIONS AND RESULTS

In the resting stage, all leads showed moderate low voltage fast (18 to 24 cycles per second) activity interspersed with brief runs of poorly organized 9 to 12 per second waves. The temporal leads showed much fast (18 to 30 cycles per second) activity, which was an artefact due to undiminished muscular tension.

Short runs of alpha activity occurred more frequently and were better organized in the frontal and motor areas than in the occipital area during

Average Amplitudes for Alpha Waves

Cortical Area	Average Amplitude, Microvolts			
	Resting Stage	After Hyperventilation		
		20 Sec.	86.3 Sec.	230 Sec.
Left frontal	46.42	Not available after hyperventilation		
Left motor	45.24	50.00	41.64	43.43
Left occipital	28.24	38.57	37.52	37.36

the resting stage of the record. Also, the alpha potentials recorded from the frontal and motor areas showed a maximum amplitude of 75 microvolts, as compared with the maximum of only 50 microvolts for the potentials from the occipital area. This is just the reverse of the usual finding, for it is the occipital areas which ordinarily show the dominant

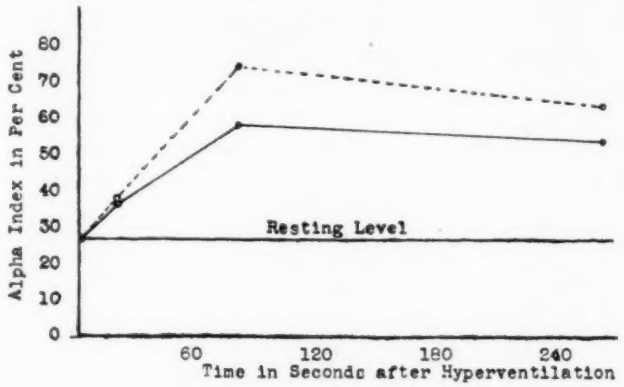

Fig. 2.—Graphic representation of sustained increase in the alpha index after hyperventilation. The solid line indicates the values for the motor lead; the broken line, values for the occipital lead.

activity. This diminished amplitude from the occipital area was constant throughout the record, as can be seen in the table.

Brief localization studies (bipolar recording) on a push-pull circuit were made but revealed no evidence of a focal lesion. After this, monopolar recording was resumed for the hyperventilation run. After three minutes of hyperventilation, no immediate build-up occurred and no seizure discharges were precipitated.

The alpha index for the resting stage of the record was 28.2 per cent. Hyperventilation tended to stabilize the record and increased the alpha activity, particularly in the occipital areas. Twenty seconds after hyperventilation the alpha index rose to 36.0 per cent in the motor lead and 36.95 per cent for the occipital lead. The alpha index reached its peak approximately 86.3 seconds after hyperventilation was concluded, at which time the alpha index was 57.3 per cent for the motor lead and 73.6 per cent for the occipital lead. Four and one-half minutes (two hundred and seventy seconds) after hyperventilation was concluded, the alpha index had decreased to 51.8 per cent for the motor lead and 61.75 per cent for the occipital lead.

SUMMARY

In the resting stage, the electroencephalogram of Helen Keller showed better organized alpha activity in the frontal and motor leads. Consistently, throughout the record, the frontal, and especially the motor, leads showed an amplitude greater than that observed in the occipital leads. Hyperventilation, which increased the alpha activity in the occipital leads, did not increase the amplitude of the potentials from the occipital areas to such an extent that they equaled in amplitude the potentials recorded from the motor areas.

Since all of Helen Keller's learning and experience is through her sense of touch or tactile discrimination, with particular emphasis on the corresponding cortical areas, it is suggested that the amplitudinal differences recorded in the electroencephalogram may be correlated with differences in the functional organization of the cerebral cortex.

LaGarde General Hospital.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Anatomy and Embryology

DEPLETIONS AND ABNORMALITIES IN THE CERVICAL SYMPATHETIC SYSTEM OF THE CHICK FOLLOWING EXTIRPATION OF NEURAL CREST. CHESTER L. YNTEMA and WARNER S. HAMMOND, J. Exper. Zool. **100**:237 (Nov.) 1945.

By means of a well controlled technic, Yntema and Hammond accomplished accurate extirpations of the neural crest from the occipital and cervical regions of chick embryos. The results indicate that the cervical sympathetic ganglionic cells arise from local neural crest. The superior cervical ganglion rudiments lie in the neural crest at occipital and upper cervical levels. Both postcarotid and paravertebral trunks are dependent on the presence of neural crest cells.

When the dorsal neural folds were included in the extirpations, the dorsal parts of the spinal cord were atypical: Definite regions of the cord were absent, or remaining parts showed pronounced overgrowth.

The preganglionic column and its fibers differentiate in the absence of neural crest and of sympathetic ganglia. Ascent of the fibers into the neck depends on the presence of sympathetic ganglia along the path. If cervical sympathetic ganglia differentiate in the absence of preganglionic fibers, these ganglia are smaller than normal.

After removal of the neural crest in the occipital and upper cervical regions, the enteric plexus about the esophagus and stomach contains few, if any, neuroblasts.

After bilateral extirpation of neural crest, rudiments of sympathetic ganglia migrate backward as much as four segments into the rostral end of the area of operation beyond the last spinal ganglion present. There is less migration into the caudal area. Less extensive depletions of spinal and sympathetic ganglia are produced by unilateral extirpation of neural crest.

REID, Boston.

DEVELOPMENT OF THE VASCULAR PATTERN WITHIN THE WALLS OF THE CENTRAL NERVOUS SYSTEM OF THE CHICK EMBRYO. JAMES F. FEENEY JR. and RAY L. WATTERSON, J. Morphol. **78**:231 (March) 1946.

Feeney and Watterson studied the development of the intraneural vascular pattern at all levels of the neural tube of the chick embryo by means of serial pyroxylin sections of embryos after injection of india ink. The embryos were examined at the 2½, 3, 3½, 4, 5, 6, 7, 8, 9, 10, 12, 14 and 16 day stages. Reconstructions were made of each region of the brain and of the cervical swelling. Other levels of the cord were studied directly from slides.

The first vessels to penetrate the neural tube (between the 72 and the 84 hour stage) enter ventrally, except in the diencephalon and the telencephalon. At the 84 hour stage vessels are seen in the cervical swelling and in all subdivisions of the brain except the telencephalon.

The slow and orderly elaboration of the vessels at the level of the cervical swelling permits the identification of fifteen distinct intraneural vessels. At this level the order of appearance of the individual vessels is remarkably constant. After the twelfth day the intraneural vessels become numerous, and it is suggested that the localized changes controlling morphogenesis become more uniform at this stage.

At the levels of the cord anterior to the cervical swelling and posterior to the lumbosacral swelling, the same vessels arise more slowly. The most posterior part of the cord has no intraneural vessels.

Although the vascular pattern within the walls of the brain evolves rapidly, the sequence of events can be recognized. Fusion of the tips of the first capillaries that enter ventrally (posterior levels) with those that enter laterally (at anterior levels) establishes a paired endoneural sinus. Other interconnections made almost simultaneously form an endoneural plexus on the periphery of the ependyma. The peripheral spread of plexus formation establishes interconnections among vessels within the mantle zone. This sequence of events is most evident in the myelencephalon. The elaboration of specialized structures may modify the basic pattern in other regions of the brain. The development of vascularity within the optic lobes is striking not only because of its regularity but because of its relationship to the stratification of the neural elements of these structures. The ectodermal walls of the epiphysis and of the pars nervosa of the hypophysis, although continuous with the walls of the brain containing intraneural vessels, are free from intraectodermal vascularity.

Vascularization always begins at a specific area in each region of the brain and spreads in specific directions. Each region of the brain seems to develop its vascular pattern independently of adjacent regions.

In the early stages of development of the brain, capillary penetrations come from the lateral surface, whereas in the cord and the myelencephalon ventral penetration of capillaries occurs first.

The most rapid and early development is that of the complex endoneural plexus on the periphery of the ependyma of the brain. The vascular plexus in the mantle zone of the brain always spreads progressively from the ependyma peripherally, while in the cord such spreading from inside to outside occurs only in the marginal zone.

REID, Boston.

Physiology and Biochemistry

THE TRANSFER OF PENICILLIN INTO THE CEREBROSPINAL FLUID FOLLOWING PARENTERAL ADMINISTRATION. WALSH MCDERMOTT and RUSSELL A. NELSON, Am. J. Syph., Gonor. & Ven. Dis. **29**:403 (July) 1945.

McDermott and Nelson studied the effect of transfer of penicillin into the cerebrospinal fluid of 70 patients with late latent syphilis and other infections of the central nervous system. The tests for penicillin activity of the cerebrospinal fluid were made by four different technics of bioassay.

With the dilution technics of bioassay, no penicillin was demonstrable in the specimens of cerebrospinal fluid obtained from 70 patients who had received penicillin in various dosages by parenteral routes. The presence of neurosyphilis and, in 1 instance, tuberculous meningitis did not alter these results.

Approximately 0.02 unit of penicillin was demonstrable in the cerebrospinal fluid of patients who had received one or two intramuscular injections of 300,000 to 500,000 units of penicillin three to four hours previously.

In concentrations ranging from 0.078 to 1.25 unit of penicillin per cubic centimeter of serum, penicillin is diffusible through artificial membranes in vitro and into ascitic fluid in vivo. Thus, the failure of the penicillin to appear in the cerebrospinal fluid is not because it is bound to a high degree to nondiffusible elements in the serum.

As a result of their studies, the authors suggest that, since the immediate results of the intramuscular treatment of syphilitic meningitis and other forms of neurosyphilis with penicillin are so promising, it is unnecessary to use the intrathecal route for the treatment of these conditions. In the treatment of purulent meningitis, on the other hand, the administration of penicillin by the intrathecal route cannot be abandoned.

GUTTMAN, Philadelphia.

CHEMICAL CHANGES IN THE CEREBRAL CORTEX ASSOCIATED WITH CONVULSIVE ACTIVITY. W. E. STONE, J. E. WEBSTER and E. S. GURDJIAN, J. Neurophysiol. **8**:233 (July) 1945.

Stone, Webster and Gurdjian studied dogs under morphine anesthesia and administered metrazol intravenously after curarizing the animals. The electrical

activity of the cortex was recorded directly. During the course of the electrical discharge of seizure type the cortex was frozen in situ and specimens were removed for examination. In 4 dogs seizure discharges occurred during morphine anesthesia and without curarization or administration of metrazol. The cortices of these animals were also frozen and portions removed for study. Oxygenation of the blood was usually studied at the time of freezing. The cerebral tissue was studied for its lactic acid, inorganic phosphorus, phosphocreatine phosphorus and adenosine triphosphate contents. During the convulsive seizure discharges following administration of metrazol or occurring spontaneously in the dog anesthetized with morphine there were an increase of cerebral lactic acid and a decrease in cerebral phosphocreatine, with an increase in inorganic phosphate. No alteration of adenosine triphosphate occurred. The cerebral chemical changes during seizures are the same as those found when the oxygen supply is deficient. The oxygen saturation of the blood in the animals studied was in no instance sufficiently low to cause the alterations recorded. Stone, Webster and Gurdjian interpret the chemical alterations of the cerebral cortex during convulsions as indicating a lag of the oxidative processes behind an increased expenditure of energy during convulsive activity.

FORSTER, Philadelphia.

THE FUNCTIONAL SIGNIFICANCE OF THE ROSTRAL CINGULAR CORTEX AS REVEALED BY ITS RESPONSES TO ELECTRICAL STIMULATION. WILBUR K. SMITH, J. Neurophysiol. **8**:241 (July) 1945.

Smith studied the effects of electrical stimulation of the rostral portion of the cingular cortex of the monkey (Macaca mulatta). Stimulation evoked a complex response involving both somatic and autonomic realms. The complete response consisted of opening of the eyes, pupillary dilatation, movements of the lips, vocalization, alterations in respiratory movements, cessation of somatic movements, relaxation of muscular tension, cardiovascular changes and piloerection. In some experiments only a part of this complex could be elicited. Responses from the two sides were identical. The responses were elicited only by repetitive stimuli. Smith points out that the cortex of the cingular gyrus in primates is divisible into two cytoarchitectural areas. The rostral portion, which was studied in these experiments, corresponds to Brodmann's area 24. There is some reason to conclude from these stimulation studies that area 24 is not homogeneous. The complex response elicited by stimulation of the cingular cortex of the macaque bears the connotation of emotional expression and thus implicates the cingular region in the emotive process. The potentiality of the cerebral cortex to produce emotional expression is thus demonstrated.

FORSTER, Philadelphia.

EFFERENT FIBERS OF THE PARIETAL LOBE OF THE CAT (FELIS DOMESTICUS). WALTER G. GOBBEL JR. and GEORGE W. LILES, J. Neurophysiol. **8**:257 (July) 1945.

Gobbel and Liles studied the cytoarchitectonics of the parietal lobe of the cat and searched for a parietospinal system. The parietal lobe was considered as a unit, and no attempt was made to differentiate the individual areas. In 14 adult cats the left parietal lobe was ablated. Areas were determined with reference to Garol's map of the sensory cortex. The animals were observed clinically for three weeks, and then killed. Serial sections of the brain and representative sections of the spinal cord were studied by means of Busch's modification of the Marchi technic. The sections of the parietal cortex removed at operation revealed it to be six layered and to present differences in the depth of the molecular layer. No Betz cells were seen. Association fibers passed from the parietal cortex to the adjacent cerebral lobes, and commissural fibers traveled by way of the corpus callosum to the opposite parietal lobe. Parietothalamic fibers terminated in the thalamic nucleus ventralis posterolateralis, the nucleus ventralis posteromedialis, the nucleus posterior and the pulvinar. Parietotectal fibers ended in the superior colliculus.

The parietal cortex was seen to send fibers through the pyramids to the spinal cord, where they accompanied the lateral corticospinal tract of the opposite side. Gobbel and Liles believe that the function of the parietospinal system is primarily one of sensitization, and since the parietospinal system arises in the part of the cortex concerned with tactile sensibility it is an excellent mechanism for the regulation of orderly motor activity.

FORSTER, Philadelphia.

ELECTROENCEPHALOGRAPHIC STUDIES IN DIABETES MELLITUS. MILTON GREENBLATT, JEAN MURRAY and HOWARD F. ROOT, New England J. Med. **234**:119 (Jan. 24) 1946.

The authors report on electroencephalographic studies on 40 patients with uncomplicated diabetes mellitus. These studies reveal no evidence of increased abnormalities in the cerebral activity in this series. Long duration of diabetes did not alter the incidence of cerebral dysrhythmia, and the administration of insulin over long periods had no apparent affect on the electroencephalogram. About half the diabetic patients who had frequent, severe reactions to insulin had abnormal electroencephalograms. The authors conclude that the electroencephalogram is of aid in the evaluation of the stability of cortical function of diabetic patients with reactions to insulin.

GUTTMAN, Philadelphia.

PHYSIOLOGIC ABNORMALITIES AND PATHOLOGIC CHANGES FOLLOWING EXPOSURE TO SIMULATED HIGH ALTITUDES. ALFRED F. GOGGIO and GEORGE H. HOUCK, War Med. **7**:152 (March) 1945.

This report is based on a study of many thousands of individual "flights" made in low pressure chambers over a period of about eighteen months by young subjects in excellent health and physical training.

After a preliminary ascent to 5,000 feet (1,500 meters), with redescent to ground level, the subjects were taken to 18,000 feet (5,400 meters), where they remained without supplementary oxygen for a period of ten minutes. Modern efficient oxygen equipment was then utilized by all, and the flight was taken to an altitude of 38,000 feet (11,400 meters) for a variable stay. A stop was also made at 30,000 feet (9,000 meters), and then redescent to ground level was accomplished. The total duration of the flight was about two and one-half hours.

At 30,000 feet nearly all subjects experienced pain in the chest and air hunger, aching pains in or near a joint and formication. These reactions are so common that the authors do not consider them in their report. Instead, they discuss the following, less usual, syndromes:

1. Neurocirculatory collapse. At 18,000 feet without supplementary oxygen approximately 2 per cent of the subjects showed a reaction characterized by decided pallor, sweating, bradycardia and a terminal fall in blood pressure, with flaccid unconsciousness. These symptoms were readily removed by the administration of oxygen or by the removal of the subject from the altitude chamber.

2. High altitude reactions. At 30,000 to 38,000 feet more severe reactions occurred, which could be classified into several groups.

(*a*) Neurologic reactions. These manifestations are extremely varied, from mild reflex changes and anesthesias to paralyses of any part of the body, hemiplegias, generalized and jacksonian seizures, aphasias, dysarthrias, homonymous hemianopsias and all manner of mental phenomena. Fortunately, provided prompt removal of the patient from the altitude chamber is accomplished, almost all these disturbances are transient, although they may be profound and extensive at the time of their occurrence.

(*b*) Myocardial damage. Definite myocardial damage, that is, alterations in electrocardiographic tracings which are observed after descent from the altitude chamber and which change toward normal progressively over a period of a week to ten days, is also extremely rare in this age group.

(*c*) High altitude shock. More important in point of numbers and of therapeutic possibilities than either of the two preceding groups, though also not common, are severe "systemic" or "collapse" reactions of the nature of true shock with hemoconcentration which develop at very high altitudes. These symptoms are visual disturbances in the nature of blurring or scotomas, nausea, vomiting, transient loss of consciousness, dull frontal or nasal headache and dizziness. Examination characteristically reveals cold extremities, indicative of poor peripheral circulation, a low blood pressure and often gray cyanosis. Examination of the blood reveals hemoconcentration, which may be progressive over a period of several hours after removal from the chamber and which when extreme appears to be accompanied with a pronounced leukocytosis. The authors report 1 fatal case.

Treatment.—Persons with the reactions of neurocirculatory collapse at 18,000 feet are benefited by an hour or so of recumbency combined with administration of oxygen. For subjects with the neurologic and cardiac types of reaction rest in bed and administration of oxygen by mask are indicated. In cases of high altitude shock patients require intravenous infusion of plasma early and in adequate amounts, controlled by clinical observation of the blood pressure and the temperature of the extremities and hematocrit readings. Oxygen therapy appears to be of definite value also.

PEARSON, Philadelphia.

THE ELECTRICAL DIAGNOSIS OF PERIPHERAL NERVE INJURY. ANTHONY E. RITCHIE, Brain **67**:273, 1944.

Ritchie studied patients with various lesions of the peripheral nerves and on each he recorded four sets of measurements: (1) the strength-duration relation of threshold electrical stimuli, including chronaxia; (2) the condenser capacities necessary for excitation; (3) the accommodation constants of the muscle during regeneration, and (4) the thresholds of excitability of the nerve-muscle complex to alternating currents of varying frequency. Neither the second nor the fourth method was found to yield consistent results; and, as the third method has been reported in detail, the author confines his observations to the first. The strength-duration relation of threshold shocks is a quantitative elaboration of the familiar galvanic-faradic test. While precise quantitative values cannot be obtained from the use of the induction coil, because of the variability in shape and amplitude of the nerves, a thermionic valve generator provides shocks of known voltage, duration and frequency, thus permitting quantitative values to be derived. Characteristic quantitative differences occur in the excitability of normal and denervated muscles. During denervation the voltage-duration curve is raised, and during the process of reinnervation it falls, so that intermediate values are obtained. Improvement of excitability appears shortly before there is clinical evidence of improvement, and hence is valuable in prognosis. While in pressure paralysis there is no change in faradic responses, minor changes occur constantly in the voltage-duration curves. The distinction which the voltage-duration curves make between normal and paralyzed muscles is in respect to degeneration of motor fibers only, and there is no distinction between wallerian degeneration due to division and that due to damage. In view of the differences in absolute values of strength-duration curves obtained with various means, the current-voltage relations in living tissues are of great importance in quantitative stimulation measurements. Because of the reactance of the tissues, stimuli of definite shape applied at the electrodes give rise to very different potential gradients across the actual excitable region.

FORSTER, Philadelphia.

Neuropathology

ON THE SUSCEPTIBILITY OF MACACUS RHESUS TO THE VIRUS OF TICK-BORNE ENCEPHALITIS. L. A. SILBER and A. K. SHUBLADZE, Am. Rev. Soviet Med. **2**:332 (April) 1945.

Silber and Shubladze studied the susceptibility of monkeys to tick-borne encephalitis. Monkeys were inoculated with brain emulsions from recent fatal

human cases of the disease and with brain emulsions of mice infected with subcultured strains of tick-borne encephalitis. All the subcultured strains killed the mice after intracerebral injection in a dilution of 1:1,000,000 and were equally neutralized with the serums of convalescent patients and with the serums of immunized rabbits. Ten per cent brain emulsions were prepared either with Tyrode's solution or with isotonic solution of three chlorides. The monkeys were inoculated intracerebrally, intravenously and intranasally and were observed three months unless they died earlier. The brain, blood, liver and spleen of the animals were examined for virus content by intracerebral inoculation of mice. The brain and other organs of the monkeys were subjected to histologic examination by A. G. Kestner. The serums of the surviving monkeys were tested for virus-neutralizing antibodies.

The authors conclude that Macacus rhesus monkeys are susceptible to the virus of tick-borne encephalitis but that the disease is not always fatal. Of 9 monkeys given inoculations in the cerebrum and spinal cord, 3 survived. Intravenous inoculation of 2 monkeys and nasal inoculation of 1 monkey proved ineffective.

The incubation period in Macacus rhesus lasts five to nine days, and the average duration of the disease is six to eleven days. The chief symptoms are fever and paralysis of the forelimbs and hindlimbs.

The disease is an acute meningomyeloencephalitis.

Serum antibodies which neutralize the virus of tick-borne encephalitis appear in convalescent monkeys. The antibodies occur late in the disease and are apparently retained in the serum for a long time after recovery. Residual paralysis of the upper extremities is seen in convalescent monkeys and resembles that seen clinically.

The virus of tick-borne encephalitis differs from that of the Japanese summer and the St. Louis type. Louping-ill occupies an intermediate position between St. Louis and the Japanese encephalitis.

GUTTMAN, Philadelphia.

A CONTRIBUTION TO THE STUDY OF DISSEMINATED ENCEPHALOMYELITIS: REPORT OF FOUR CASES PRESENTING THE MANIFESTATIONS OF BOTH NEUROMYELITIS OPTICA AND ALBUMINOCYTOLOGIC DISSOCIATION, ONE WITH NECROPSY FINDINGS. CLEMSON MARSH and SHERMAN S. DEVINE, Bull. Los Angeles Neurol. Soc. **10**:35 (March-June) 1945.

Marsh and DeVine studied 4 patients who had evidence of both neuromyelitis optica and albuminocytologic dissociation. Necropsy, performed on 1 of the patients, revealed that the central lesion was a demyelinating process involving the peripheral nerves, the spinal cord and the optic chiasm. The white matter of the brain itself seemed to have escaped the process. There was, however, widespread infiltration of the leptomeningeal space and the spinal cord with lymphocytes, suggesting a degree of meningeal reaction. It is of interest that with this lymphocytic reaction, lumbar puncture revealed no pleocytosis.

At present there exist some confusion of terminology, variation in clinical impressions and incomplete agreement as to the histologic changes associated with this syndrome. Some investigators believe that neuromyelitis optica is a toxic-infectious process; others, that it is a virus infection, and others, that neuromyelitis optica, acute multiple sclerosis and disseminated encephalomyelitis cannot be segregated, either clinically or pathologically. Most pathologists believe that there is no conclusive evidence which shows the precise relationship of these conditions.

Marsh and DeVine conclude that "the occurrence of these various common clinical manifestations together with albuminocytologic dissociation found in each of these four patients at one time or another during the course of the illness constitutes presumptive evidence that neuromyelitis optica, Guillain-Barré syndrome and disseminated encephalomyelitis may in some circumstances be caused by the same etiologic agent."

GUTTMAN, Philadelphia.

EXPERIMENTAL TUBERCULOSIS OF THE SPINAL CORD IN A RABBIT. LUCIANO SCHWARTZ, Rev. neurol. de Buenos Aires **8**:362 (Oct.-Dec.) 1943.

Schwartz injected tubercle bacilli into the subarachnoid and suboccipital spaces of 4 rabbits, which survived twenty-three days, fifty-six days, one month and four months, respectively. Human and bovine tubercle bacilli were used, in varying doses. Tuberculous infection, including meningitis, meningomyelitis, radiculitis, ganglionitis and tuberculomas, was observed in all 4 animals. Maximal involvement was noted in the region of the cauda equina, with predominant paralysis of the hindlimbs. In 1 of the animals inoculated with bovine bacilli, a tuberculoma, 2 mm. in diameter, was observed in the periphery of the lumbar portion of the cord. The tuberculous infiltration extended from this caseous focus and involved the anterior root, the anterolateral tract and part of the anterior horn. In the experimental production of tuberculoma of the central nervous system in rabbits, the duration of infection and the quality and the dose of the bacilli injected play a role.

N. SAVITSKY, New York.

Diseases of the Brain

THE SYMPTOM OF "ELECTRICAL DISCHARGE" IN BRAIN INJURIES. A. V. TRIUMFOV, Am Rev. Soviet Med. **2**:350 (April) 1945.

Triumfov reports his observations on 2 patients who had the sensation of "electric current" up and down the spine after injury.

One of the patients had had a fracture of the sixth cervical vertebra. He had quadriplegia, which subsided in a few days, with recovery of function within a month. The sensation was described as follows:

"Whenever I bend my head I feel that something is running quickly down my neck and along the spine. If I bend my head still further, this sensation reaches my arms and legs; it is not painful, but unpleasant. The sensation disappears just as soon as I raise my head. Occasionally my arms and especially my fingers become weak; if I hold anything in my hands, I drop it. I must watch my head and hold it upright."

The intensity of this phenomenon lessened gradually, and a month later the patient experienced the sensation of "electric current" down his spine and in his lower extremities only with abrupt bending of the head. The intensity of the sensation was negligible; there was no weakness of the hands. A month later the symptom had disappeared altogether, and no further signs of involvement of the nervous system were noticed. In the course of the war Triumfov encountered a number of cases in which a similar sensation was experienced in bending the head and body forward after injuries of the brain, but not of the spinal cord.

Further studies were made on 23 cases. In 7 cases the wound was located in the occipital region; in 5, in the parieto-occipital region; in 5, in the parietal region; in 2, in the temporal region; in 2, in the temporoparietal region, and in 2, in the coronal region. In 20 cases the dura mater was known to be involved.

A second patient had wounds in the right occipitotemporal region from mine fragments. The dura had been injured. Two or three weeks after complete healing of the wound (three months after the injury) the patient noticed that whenever he bent his head forward, especially with the simultaneous bending of the entire body, he experienced the sensations of an "electric shock" passing down his spine and arms If he happened to touch an object with his finger tips, he felt an electric current These paresthesias could not be described by the patient other than as a sensation produced by an "electric current." In his own words, "It is very similar to it." Occasionally he felt, at the same time, weakness of the wrists, particularly the right one (injury to the right occipitotemporal region). This symptom was recorded during a period of one and a half to two months, and decreased gradually. No other sign of injury to the nervous system was observed.

The symptom is purely subjective. So long as the sensation was paresthetic, and not painful, no signs of suffering, such as dilatation of the pupils or changes in the pulse or breathing, were observed.

In the majority of cases the history pointed to signs of meningeal irritation; only in isolated cases were the paresthesias observed against the background of residual meningeal manifestations. Most often the symptom was observed as an isolated phenomenon. Characteristically, its onset was either simultaneously with the healing of the wound or two or three weeks after the wound was healed.

The practical importance of this symptom of "electrical discharge" (*décharge électrique*) is worthy of emphasis. Arising late, often in an isolated form, when other changes of the nervous system are no longer present, and after the wound is healed, it can greatly restrict the efficiency of patients and their ability to engage in military service. In a number of patients the symptom is so intense that the head is held in a fixed position to avoid bending it. The "weak point" of this symptom from the point of view of military examination lies in its subjective nature. However, the sensation experienced by patients is extremely characteristic and is described by them, always in the same way, without leading questions. By persons experienced in electrical work it is never described otherwise than as the sensation produced by an electric current.

It is possible that the peculiar paresthesia reflects injury to the posterior nerve roots of the spinal cord, and occasionally also to the anterior roots, as indicated by the simultaneous weakness of the extremities. It may perhaps be assumed that the symptom is caused by the formation of scar tissues and adhesions in the meninges. It develops gradually and disappears just as gradually, the duration averaging one to two months. Recovery is hastened by therapeutic physical exercise, such as training in the gradual forward bending of the head and body. The symptom is much more pronounced and is more frequent following injury to the brain and spinal cord than it is in disseminated sclerosis.

GUTTMAN, Philadelphia.

CASE OF AMNESIC APHASIA WITH FOCAL LESION IN AREA 37. R. R. WILLIAMS. Bull Los Angeles Neurol. Soc. **10**:75 (March-June) 1945.

Williams reports on the case of a man aged 67 who was admitted to the hospital because of a "stroke." About three months prior to his admission the patient was treated for "a heart attack." He was confined to bed, and on the morning of the third day he had a "stroke without loss of consciousness but associated with paralysis of the right limbs." At first he was unable to speak, or even to swallow. In about a week the hemiparesis and other signs began to subside. The patient was left with inability to find his words in talking. The residual speech defect was a classic amnesic type of aphasia, with loss of recall of the names of objects and concepts. The patient spoke with circumlocutions; e. g., for "key" he said, "It is to open a door with." At the time of admission to the hospital he was confused, the result of a recent cerebral vascular lesion. Gangrene of his lower extremities developed. He died three days after admission to the hospital.

A lesion in area 37 of Brodmann was suspected, and the brain was sectioned horizontally through Broca's convolution and Wernicke's area. This section revealed only one small lesion, in the left optic radiation bordering on the posterior horn of the ventricle. A section 1 cm. higher and parallel to the first passed through a thrombotic area of softening, 1 cm. in diameter, located directly in area 37. Other sections showed small thrombotic lesions in the centrum semiovale on the left side and in area 6 on the right side.

The vascular supply of area 37 of Brodmann is peculiar in that it is from the third temporal branch of the middle cerebral artery, as well as the posterior cerebral artery. Focal lesions of vascular origin in this region are rare. In the present case the area of cortical involvement was small, but evidently the subcortical spread of the lesion had interrupted the corticopetal fibers in this region, which have to do with recollection of the names of objects. The history of an amnesic type of aphasia in the presence of a sharply circumscribed lesion makes this case one of interest in the study of focal lesions associated with aphasia.

GUTTMAN, Philadelphia.

THE SYNDROME OF PHYSICAL OR INTRINSIC ALLERGY OF THE HEAD: III. VASOMOTOR RHINITIS AND THE VASODILATING PAIN SYNDROME; THEIR RELATIONSHIP TO MYALGIA AND ENDOLYMPHATIC HYDROPS (MÉNIÈRE'S DISEASE). H. L. WILLIAMS, Proc. Staff Meet., Mayo Clin. **21**:58 (Feb. 6) 1946.

Williams attempted to determine whether association of the four symptom complexes—myalgia, vasodilating pain, endolymphatic hydrops (Ménière's disease) and vasomotor rhinitis—was frequent enough "to be attributed to some factor other than chance." He studied 362 cases in which one of these diagnoses had been established. In 122 of these cases, or in more than one third, some association of two or more of the syndromes was apparent. The factor in common appears to be mechanical, physical or intrinsic allergy. The symptoms of the various conditions can be relieved by nicotinic acid in a large percentage of cases.

ALPERS, Philadelphia.

MALARIAL PAPILLITIS. ROBERT B. LEWY, War Med. **7**:341 (June) 1945.

Papillitis of the optic nerve is a common concomitant of recurrent malaria. The mechanism of this process is unknown, but the condition probably does not result from medication.

PEARSON, Philadelphia.

FAMILIAL TUBEROSE SCLEROSIS WITH CALCIFICATION. JOHN APLEY, Brain **67**:258, 1944

Apley presents 2 cases of tuberous sclerosis occurring in father and son. The father, who was examined at the age of 36, gave a history of the appearance of seizures and cutaneous lesions at the age of 6 years. Examination revealed that he was of average intelligence, but rather slow of speech, and had an adenoma sebaceum of typical butterfly distribution. A roentgenogram of the skull revealed scattered calcifications. Ophthalmoscopic examination disclosed a gray mass of mulberry appearance at the nasal edge of the left optic disk. The son, aged 5 years 9 months, had had seizures since the age of 15 months. He presented evidence of mental and moral aberration. Cutaneous lesions, resembling adenoma sebaceum, had appeared. Roentgenograms of the skull at the age of 3 years were normal, but those at the age of 5 years 9 months demonstrated several small opacities.

FORSTER, Philadelphia.

PNEUMATOCELE DUE TO FRONTAL TRAUMA. P. W. LONGO, A. M. PIMENTA and F. P DE AQUINO, Arq. de neuro-psiquiat. **3**:52 (March) 1945.

A man aged 47 was kicked by a horse in the right frontal region, after which he was unconscious for an hour and bled from the nose a few hours later. The next day he was dull and had no appetite. He remained in this state for eight or ten days, when he suddenly complained of severe headache. At the same time there was a watery secretion from the nose. About twenty-five days after the accident he became confused and remained so for four days. Examination one month after injury showed an intermittent flow of clear and bloody fluid from the nose and probable diminution of smell; neurologic examination revealed nothing abnormal. The mental examination showed disorientation, recent memory defect, impairment of sleep rhythm and irritability. Roentgenograms of the skull showed a pneumatocele in the right frontoparietal region with no air in the ventricle; there was no fluid level. The air was definitely present in the intracranial cavity. There was a comminuted fracture of the posterior wall of the right frontal sinus, the roof of the orbit and the right ethmoid bone. There was also a fracture of the nose. Suboccipital puncture showed clear fluid and about 24 cells per cubic millimeter, of which 68 per cent were lymphocytes; the chlorides measured 720 mg. and the albumin 20 mg., per hundred cubic centimeters; the Wassermann reaction was negative. The destroyed bone was removed from the region of the right

frontal sinus. Five cubic centimeters of air was aspirated at the site of a very small defect in the dura. Thirty-six days after the operation no air was seen in the intracranial cavity, and there was striking subjective improvement.

N. SAVITSKY, New York.

ACCIDENT WHICH MIGHT HAVE BEEN ASCRIBED TO PNEUMOENCEPHALOGRAPHY. JULIO A. GHERSI, Prensa méd. argent. **33**:528 (March 8) 1946.

Ghersi reports the case of a woman aged 36 with bitemporal hemianopsia and atrophy of the optic nerve. She was to enter the hospital for air studies to verify the existence of a chiasmal lesion. A few hours before admission, while at home, she suddenly lost consciousness and died. Autopsy revealed an intracranial aneurysm of the internal carotid artery, 4 cm. in diameter; it had ruptured on the day she was supposed to have had the pneumoencephalographic examination. The author reports this case to emphasize that many of the alleged accidents of encephalography are due to the underlying condition. He points out that if rupture of the aneurysm had occurred a few hours later it would have been considered a complication of pneumoencephalography.

N. SAVITSKY, New York.

Treatment, Neurosurgery

ACUTE ALCOHOLISM TREATED WITH INSULIN. SIDNEY TILLIM, Am. J. Psychiat. **101**:396 (Nov.) 1944.

Tillim reports 4 cases of acute alcoholism occurring in military personnel in which the condition was treated with injections of insulin. The symptoms varied and consisted of hyperirritability, insomnia, loss of appetite, tremor of the hands and excessive smoking. An initial dose of insulin was given which would produce somnolence, thirst and diaphoresis in one to one and a half hours. The amount varied from 40 to 80 units. A second dose was administered if the first failed to be effective in one hour. In the event of an excessive dose, "fractional neutralization" by intravenous injection of dextrose (5 to 10 Gm.) was employed to produce the desired effect. The treatment continued from two and one-half to three hours and was terminated by oral administration of 8 fluidounces (250 cc.) of fruit juice with an additional ounce (30 Gm.) of sugar. The number of treatments varied from one to four, as needed in the first twenty-four hours. Sedatives were used only sparingly.

Tillim maintains that his method of insulin therapy is superior to others in treating acute alcoholism, in that it shortens the period of disability and is acceptable to the patient. In his method, he is in no hurry to neutralize the insulin reaction, he gives a larger initial dose of insulin and he maintains a good intake of water.

BORKOWSKI, Philadelphia.

TRANSURETHRAL RESECTION OF THE VESICAL NECK IN MANAGEMENT OF CORD BLADDER. JOHN L. EMMETT, Proc. Staff Meet., Mayo Clin. **21**:102 (March 6) 1946.

A previous study by Emmett revealed that in 13 cases of transverse lesion of the spinal cord with retention of urine transurethral resection of the vesical neck was followed by excellent results in 8 cases, by improvement in 2 cases and by no improvement in 3 cases. Emmett reports another case in which a similar procedure produced excellent results in bladder function after a transverse syndrome of the spinal cord resulting from injury.

ALPERS, Philadelphia.

UNILATERAL FACIAL PARALYSIS: CORRECTION WITH TANTALUM WIRE. J. E. SHEEHAN, Lancet **1**:263 (Feb. 23) 1946.

Sheehan reports on the treatment in 8 cases of unilateral facial paralysis with tantalum ribbon and wire. The thicker ribbon was found preferable, as it

immobilized the parts better and tended less to give under the stress of facial motion. The author describes the technic as follows: After the usual preparation, the paralyzed side of the face is anesthetized with 1 per cent procaine hydrochloride, and a curved incision 2 inches (5 cm.) long is made over the temporal muscle above the zygoma and behind the hair line. The temporal fascia is exposed. A long, curved, 18 gage Weck needle is inserted into the lower part of the incision and passed downward between the skin and the mucosa to 8 mm. beyond the midline of the chin, where it emerges. During its course the needle intermittently takes deep bites of tissue. One end of a loop of tantalum wire (or ribbon) is passed through the bore of the needle, which is then withdrawn, carrying the strand of wire back with it to the incision in the temporal area. A second needle is inserted 1 cm. above the first one and follows its course 1 cm. above it. The other end of the loop of tantalum wire is passed through the bore of this needle and is carried back. A vertical incision is made on the chin to connect the upper and lower wires, and the skin on either side is undermined slightly. Tantalum foil is rolled around the loop to prevent the wire from breaking through the tissues, and the incision is closed with ophthalmic gut.

The same procedure is carried out at the angle of the mouth and on the upper lip. In the first instance, the loop is affixed 0.5 cm. from the corner of the mouth. In the second, the lower needle follows the course of the vermilion border to 6 mm. past the midline; the upper needle runs just beneath the base of the nose, so that the pull of the wire helps to straighten the nose.

The three sets of wire (or ribbon) in the temporal incision are then pulled to overcorrect the face slightly and are held in position with clamps. The ends of each set are twisted together; any excess is cut off, and the ends are deeply embedded in the temporal muscle and fascia.

To support the upper eyelid, a needle of shorter design is inserted at the upper portion of the temporal incision and passed under the upper orbital rim, downward and forward, to emerge over the attachment of the internal lateral ligament. A second needle, inserted 1 cm. below the first, takes a course following the lower lid and emerges beneath the attachment of the internal lateral ligament. One end of the wire or ribbon loop is inserted in the lower needle, and a vertical incision, exposing the internal lateral ligament, is made to join the upper and lower wires. The other end of the loop is then inserted in the upper needle, and both needles are withdrawn, leaving the loop moored in the internal lateral ligament. From this point the procedure is the same as for correction of the mouth. When the set of wires supporting the eyelid is securely embedded in the temporal muscle and fascia, the temporal incision is sutured, and sterile bandages are applied. The period of detention in the hospital is brief, twenty-four to seventy-two hours in all. The author concludes that this method is superior to those discredited methods of repair which join nerves of different numbers, producing a slight twitching of the facial muscles at best. In contrast to them, traction with tantalum ribbon or wire appears both to support and balance the face and to overcome the antagonistic pull of the muscles on the unparalyzed side. It seems useful either as a permanent support or as a temporary one, during the regeneration of a nerve, in which case the wires can be removed after recovery.

YASKIN, Camden, N. J.

SUBARACHNOID ALCOHOL INJECTIONS FOR TREATMENT OF PAIN ACCOMPANYING PELVIC NEOPLASMS. O. B. NESTAREZ and S. C. FRANCO, Rev. neurol. e psiquiat. de São Paulo **10**:3 (Sept.-Oct.) 1944.

Nestarez and Franco report 16 cases in which they employed the method of Dogliotti for the relief of pain resulting from neoplasms of the cervix which extended into the pelvis. The patients complained of severe pain in the lower limbs, abdomen and back, which could not be controlled with other methods. The injections were made with the patient lying in a lateral position, and tilted about 45 degrees ventrally. The site of injection was elevated somewhat, and from 0.4 to

1.5 cc. of absolute alcohol was injected slowly, during periods up to one minute. Each patient was kept in the original position for periods varying from two to four hours. A patient with complicating paralysis of one lower extremity was kept in this position for only ten minutes. The patients were later placed in a ventral position, with the head lowered somewhat, for about twenty-four hours. The injections were all made into the lumbar subarachnoid space. In 2 cases two and three injections were given, respectively. The interval between injections was somewhat less than ten days in 1 case and three months in the other. There were complications in 4 cases, with paralysis of the right lower extremity in 1 case and retention of urine in 3 cases. Good results were obtained in 7 cases, the pain stopping in 1 case for about six months. There was some improvement in 2 cases and transitory relief in 1 case. The period of survival in this series ranged from one to six months.

N. SAVITSKY, New York.

Encephalography, Ventriculography, Roentgenography

NOTES ON THE PATHOLOGY OF CRANIAL TUMORS: I. OSTEOMAS OF THE SKULL, WITH INCIDENTAL MENTION OF THEIR OCCURRENCE IN THE ANCIENT INCAS. KENNETH H. ABBOTT and CYRIL B. COURVILLE, Bull. Los Angeles Neurol. Soc. **10**:19 (March-June) 1945.

Abbott and Courville report on osteomas of the skull, which are probably the most common of all new growths involving the cranium. However, osteomas are relatively rare, especially those which are sufficiently large to necessitate surgical attention. This type of tumor has been recognized since the time of Galen. It is stated that the incidence in the larger neurosurgical clinics is approximately 1 per cent.

Osteomas of the skull are classified into four types: (1) circumscribed osteomas of the cranial vault; (2) diffuse osteomas, arising most commonly from the sphenoid or temporal bone; (3) osteomas of the orbitoethmoidal or orbitomaxillary region, and (4) osteochondromas of the cranial floor.

The circumscribed osteomas of the cranial vault may be subdivided into (1) the small, and usually subclinically, osteoma eburneum, which arises by a broad base with either an indistinct or a sharply circumscribed border, and (2) osteoma spongiosum, which is a larger, more rapidly growing tumor and has a central portion of cancellous bone. The latter tumor sometimes becomes large and pedunculated and requires surgical excision, especially when the inner table of the skull is eroded and some degree of pressure on the underlying structures results in neurologic symptoms.

The diffuse osteomas, arising most commonly from the greater wing of the sphenoid bone, from the petrous portion of the temporal bone or, more rarely, from the orbital roof, are unusual, slowly growing tumors, the orbital type of which often produces exophthalmos and casts a dense paraorbital shadow on the roentgenogram. They are usually amenable to surgical excision.

The orbitoethmoidal (or orbitomaxillary) osteomas are said to have their origin in cartilaginous rests which persist in the line of the frontoethmoidal (or maxilloethmoidal) suture line. These tumors may have a complex localization, invading in their growth two or more of the regional cavities (orbit; frontal or ethmoid sinus, or cranial chamber), or they may be confined within a single cavity, as a result of eccentric growth from a well defined focus. Within such a cavity, the osteoma may become completely detached from its pedicle, resulting in the formation of a "dead osteoma," which is biologically inert.

Osteochondromas arising from the cranial floor are extremely rare growths, but, because of their upward extension into the intracranial space, they are to be classified as one of the many possible tumors which may compromise the intracranial space.

The available facts regarding their location and development suggest that osteomas are the result of some perversion in the union of the suture lines, possibly with the formation of isolated cell rests of osseous or cartilaginous character.

GUTTMAN, Philadelphia.

Congenital Anomalies

CAUSATION OF MONGOLISM. M. ENGLER, J. Neurol. & Psychiat. **7**:27 (Jan.-April) 1944.

Engler investigated 113 cases of mongolism and found the following exogenous factors to be significant in its causation: In 6.8 per cent of cases there was a considerable degree of ill health or nervousness in the mother during gestation; in the majority of cases the mongolian imbecile was the last born of a rather large family and the age of the mother was usually advanced; in 12.7 per cent an induced miscarriage through abortifacients or curettage occurred immediately before the birth of the mongolian imbecile. The author concluded, on the basis of morbid heredity, that the unhealthy condition of the mucous membrane of the uterus at the time of implantation of the impregnated ovum was the chief cause of mongolism and that one of the main factors contributing to this unhealthy condition was miscarriage.

MALAMUD, Ann Arbor, Mich.

STURGE-WEBER DISEASE. TOBIAS BRAVO and FERNANDO LOAYZA, Rev. neuro-psiquiat. **6**:317, 1943.

The authors report the first case of Sturge-Weber disease (nevoid amentia) in the Peruvian literature. They were unable to find a similar case in the "American literature." They record the case of an unmarried woman, aged 43, who was admitted to the hospital because of seven convulsive seizures in one day. There was a history of convulsive attacks from the first to the fifth year of life. She had had no attacks for sixteen years.

Examination showed an extensive nevus on the right side of the face, some mental retardation and intracranial calcification. The neurologic examination showed hyperreflexia, a positive Babinski sign, diminished abdominal reflexes and adiadokokinesis, all on the left side. There was no glaucoma. The nature of the seizures suggested a functional or hysterical component.

SAVITSKY, New York.

Society Transactions

PHILADELPHIA NEUROLOGICAL SOCIETY

Robert A. Groff, M.D., *Presiding*

Regular Meeting, April 26, 1946

Remedial Procedures for Handling Aphasic Patients. Dr. Lou Kennedy (by invitation).

A veteran, aged 26, was first seen in September 1945 at the neurophysical rehabilitation clinic, at which time he presented (1) motor aphasia which was complete except for two nonsense syllables and (2) sensory aphasia of sufficient severity to prevent his understanding of all but simple commands.

The patient, who was left handed, received a severe injury to the right side of the brain on Aug. 8, 1943, while in line of duty at an Army camp. After the injury, he remained unconscious for three weeks, talking in delirium during the initial three days of his unconsciousness. Five days after the accident he became very ill, had a temperature of 107 F., was paralyzed on the left side and stopped all talking. At the end of two months he began to walk, dragging the left leg; a month later he began to vocalize, but not to form words. He was discharged with full disability after three months' hospitalization in a base hospital.

During the twenty-two months between his discharge in 1943 and his admission to the neurophysical rehabilitation clinic, he regained the use of his left leg and became fairly skilful in the use of his right hand; but, in spite of two attempts at speech therapy, covering in all a ten week period, he regained no speech.

Studies of the spinal fluid showed pressure of 12 mm. of mercury. A pneumoencephalogram, made by Dr. Temple Fay on Sept. 28, 1945, showed diffuse subarachnoid fibrosis with dilatation of the ventricles and enlargement of the cistern at the base. On the right side there was definite enlargement of the ventricle of focal porencephalic type, which corresponded in location approximately to the area of Broca. The cortical markings could not be visualized above the level of the sylvian fissure.

Dr. Fay made an exploratory trephination in order to establish the cortical lesion by direct observation. He reported the presence of a thin subdural clot, which had become organized and partly adherent to the dura over the cortical surface. There were many small pools of fluid with patches of subarachnoid adhesions, so that some cortical atrophy was present. The sulci were enlarged and the fluid spaces filled, although they had not been clearly demarcated on the pneumoencephalogram, owing, it was thought, to the presence of diffuse subarachnoid adhesions. After the opening of the areas of accumulated fluid in and about the speech zone on the right, the patient made an uneventful recovery from the operative procedure.

The speech program followed a rigid routine of three daily periods of one hour each. Emphasis was placed on the maintenance of rapport between the speech therapeutist and the patient. A combination of the phonetic method and an association building approach proved effective. Until recently all speech work was carried on in front of a mirror. At first, speech was limited to imitation of the instructor's sound units, words and sentences. Now, the patient asks and answers questions, introducing many new words. The patient showed notable progress in speech comprehension and in utterance, improvement in social adaptation and, of late, an awakening interest in practical considerations. An unexpected aspect of his therapy was the need to emphasize the phonetic, rather than the word association, method. Expected features of the case were perseveration, dysarthria and slowness of utterance.

DISCUSSION

DR. TEMPLE FAY: I should like to demonstrate the encephalograms of Dr. Kennedy's patient. It is interesting that the patient is left handed, and that the apparent defect is very close to the zone of Broca, in the right frontal area. In order to establish the character of the lesion, I made an exploratory trephination on the right side and encountered a thin capsule of what had been a well organized subdural hematoma, not attached to the arachnoid. A great deal of arachnoidal fibrosis was present, with pools of fluid. After drainage of the subarachnoid spaces and some subdural drainage, the patient was referred to Dr. Kennedy. During therapy he has been maintained on a restricted fluid intake. Dr. Kennedy has rehabilitated speech in this patient out of a total loss of speech. In the present case it has required about eight months, with three hours of treatment each day. For two years after his discharge from the Army, the patient had no speech at all except "uh huh" and "unh unh."

DR. MICHAEL SCOTT: Dr. Fay stated that he saw a subdural hematoma on the right side and the pneumoencephalogram showed a dilated ventricle on that side without any shift of the ventricular system to the side opposite the lesion. Since in most cases of subdural hematoma a shift of the ventricular system occurs, what does Dr. Fay believe to be the reason for this dilatation and absence of shift?

DR. TEMPLE FAY: The thickness of the hematoma capsule encountered was inconsequential. It did not amount to more than ¼ inch (0.6 cm.). The film shows that the anterior portion of the horn was bulging at the area of Broca. That is not common in my experience. I believe it may have had something to do with the direct lesion on the right side. I understand that the patient was struck on that side.

DR. A. M. ORNSTEEN: The title of this report is "Remedial Procedures for Handling Aphasic Patients." Apparently, they include surgical measures. I am interested in knowing whether the credit for improvement in speech belongs to the surgical procedure or to the training. What was the interval between operation and speech training? How much improvement would have taken place after the operation without speech training, and how much improvement would have taken place with speech training without operation?

I should also like to know whether there was any improvement, and how much, in the year following the patient's discharge from the Army, and before the operation, since his postoperative improvement was so great. How long has it been since you operated, Dr. Fay?

DR. TEMPLE FAY: I operated in October.

DR. A. M. ORNSTEEN: A number of months. I should like to know the comparative postoperative improvement and whether the preoperative status was changed. In order to evaluate the remedial procedures of speech training, psychologic and otherwise, in a case of this sort in which an operation is performed, there must be an interpretation of the status before operation and that after operation. It should also be decided what improvement was to have been expected from the operation alone and whether the pedagogic-psychologic procedures would have done anything without the operation.

To sum up this case report of remedial procedures for handling aphasic patients, I think Dr. Fay ought to express an opinion on this point.

DR. SAMUEL A. ZERITSKY: Overseas, my colleagues and I treated very successfully the regressive psychoneurotic patients exhibiting mutism with sodium amytal narcosis. Out of scientific curiosity, sodium amytal was administered intravenously to 5 soldiers with true organic aphasia due to cerebral injuries. In 3 of these patients we obtained striking results in that during the very period of injection they uttered several distinguishable words, whereas prior to administration of the drug they had never produced any verbalization. I, therefore, wish to suggest that the severe anxiety resulting from a sense of frustration brought on by the aphasic

impediment retards the process of relearning. Perhaps several sessions under "narcosis" will prove a useful adjunct to the course of schooling.

DR. JOSEPH C. YASKIN: Apropos to Dr. Zeritsky's comment, it is well known that an aphasic patient will utter words when emotionally aroused. Many hemiplegic patients will swear brutally in anger, and they can even lift their paralyzed arms under certain emotional excitement, especially in yawning. It is conceivable that sodium amytal may have a similar effect. However, I do not believe that this is the mechanism of reeducation. Dr. Kennedy has done an important piece of work, and it should be encouraged, for undoubtedly there will be many patients with aphasia due to trauma, a type for whom education is worth while. Even for some of the older aphasic patients, with such lesions as embolism and other nonprogressive conditions, education is important. I know from my personal experience that there are too few persons willing, or at least able, to do this type of work.

DR. ROBERT A. GROFF: Dr. Fay, do you think that in your patient Broca's area is being reactivated, or is the training he is receiving creating a new speech center?

DR. TEMPLE FAY: Dr. Zeritsky asked about the use of sodium amytal. It was not used in this case, but I was convinced that the patient had a true organic aphasia.

My surgical work after the encephalographic study was chiefly to verify the condition of the cortex, in view of what I knew Dr. Kennedy might have to do in trying to rehabilitate this man. I did not want to place on her schedule a patient whose cortex had been so destroyed that there might be no chance to bring back speech activity. Certainly, the way his speech has returned indicates to me that it is not a matter of recall alone; you notice how the speech is broken into syllables, like children's when they begin to talk, and is not in entire words.

Dr. Yaskin refers to the familiar emotional outburst in aphasic patients. We have not been able to get this patient to swear. It seems he has scruples against it.

Dr. Kennedy deserves much credit for synthesizing word mechanisms back to an expressional level. The patient's understanding of the word is complete; so the credit for his improvement was not due to operation alone. I think it belongs to Dr. Kennedy and her speech therapy program.

DR. A. M. ORNSTEEN: May I insist on an answer to my questions? Dr. Fay says he verified the condition of the cortex. I do not believe he operates for verification. He did not just take a look. Didn't you do something with the cortex, the fibrosis or the membrane, Dr. Fay?

DR. TEMPLE FAY: I did the Alexander operation of fenestration. I don't know whether it has a record for a high percentage of recoveries.

DR. ROBERT A. GROFF: I am afraid that it has not.

DR. A M. ORNSTEEN: Do you think you did anything to the circulatory area?

DR. TEMPLE FAY: I believe I gave it better circulation.

DR. A. M. ORNSTEEN: Do you think the patient's verbalization would have improved as a result of that operation?

DR. TEMPLE FAY: I don't think so. I think he would have gained something, but nothing like what we have seen here.

DR. A. M. ORNSTEEN: All right; that is the answer. I wanted your opinion.

DR. JOSEPH C. YASKIN: Several years ago a right-handed patient, after the removal of a tumor in the left cerebral hemisphere, showed stuttering and aphasia, the former predominating. I seriously questioned the existence of aphasia in this patient, but Dr. Groff was emphatic in stating that he was aphasic. Eventually the man recovered. Several weeks ago I saw a young man of a definitely neurotic makeup in whom a severe stuttering and questionable aphasia developed. At the moment I did not know whether the disturbance was organic or functional. Two days later complete hemiplegia developed on the right side, and I learned sub-

sequently that in early in life he had been a bad stutterer. The case presented by Dr. Kennedy is therefore of great interest, since the patient shows much hesitancy in speech in association with his aphasia. I wonder whether Dr. Kennedy can inform me whether or not this patient was a stutterer.

DR. LOU KENNEDY: He was a stutterer, but not in recent years. He stopped stuttering at the age of 16.

DR. MILTON MYERS: Was the patient taught to use his right hand rather than his left in school? It is well known that in some cases stuttering develops from interference with a naturally right-sided brain. According to modern ideas, teachers do not recommend that the pupil be made to use the right hand.

DR. LOU KENNEDY: The patient indicates that his teachers attempted to have him use his right hand for penmanship. Since he did not cooperate, they allowed him to continue writing with his left hand.

Parkinsonian-Like Tremor and Cogwheel Rigidity in a Child Secondary to Massive Ependymoma of the Frontal Lobe and the Caudate Nucleus; Prefrontal Lobectomy, with Cessation of Tremor and Rigidity. DR. MICHAEL SCOTT.

In the past many theories have been advanced as to the neural pathways innervated by lesions causing parkinsonian tremor. On the basis of these neurophysiologic concepts, many investigators (Horsley, 1909; Sachs, 1935; Foerster, 1936; Buch, 1940; Putnam, 1940; Klemme, 1940; Meyers, 1940) have advocated neurosurgical procedures for the relief of these tremors. These operations have included removal of area 4, areas 4 and 6, area 6 alone, section of the head of the caudate nucleus and the ansa lenticularis and section of the corticospinal tract in the cervical portion of the cord. For a complete survey of these theories and procedures, the reader is referred to the report of the Association for Research in Nervous and Mental Diseases (Diseases of the Basal Ganglia, *A. Research Nerv. & Ment. Dis., Proc.* (1940) **21**:1, 1942) and to the splendid monograph edited by Paul C. Bucy (The Precentral Motor Cortex. Illinois Monographs in Medical Sciences, vol. IV, Chicago, University of Illinois Press, 1944). In April 1943 I presented before the Philadelphia Neurological Society (Cerebral and Spinal Operations in a Case of Severe Postencephalitic Tremors, ARCH. NEUROL. & PSYCHIAT. **52**:108 [Jan.] 1944) a comparison of the results of operation on the brain and spinal cord of a patient with severe constant bilateral parkinsonian tremors. Cortical area 4 and part of area 6 of the arm center of the right cerebrum were extirpated for the relief of the left-sided tremors, and four months later the corticospinal tract at the third cervical segment on the right side was sectioned for the relief of the right-sided tremors. The tremors were abolished on both sides. One year after the first operation, the left upper extremity showed extensive flexor contracture and was useless. The right hand was held in an extensor pattern. The movements were like the fins of a fish, and the fingers would perform only simple flexor and extensor movements, such as carrying a glass of water to the mouth.

The present case is reported with the hope that it may throw light on the problem of the etiology and treatment of the classic parkinsonian tremor.

REPORT OF A CASE

E. A., a girl aged 4 years, was referred by Dr. Francis Zamborski to the pediatric service of Dr. G. E. Pratt, at the Northeastern Hospital, Philadelphia, in November 1944, because of vomiting, headaches and pronounced tremor and weakness of the right upper extremity. The child was well until September, when headaches and occasional vomiting occurred. In October a gastrointestinal study was made and revealed nothing significant. In early November, tremors of the right upper extremity developed, the headaches and vomiting increased, and the child was admitted on November 14, approximately two months after the onset of symptoms.

The past history was not remarkable. The child was alert. The head was 21¼ inches (54 cm.) in circumference, and the anterior fontanel was elevated. The left pupil was slightly larger than the right, but both reacted well. There were bilateral weakness of the sixth nerve, more pronounced on the right, and impairment of vertical gaze. The visual fields showed no impairment in the finger test, and a choked disk of 3 to 4 D. was observed.

There was slight weakness of the muscles of the lower right side of the face. The tongue was protruded in the midline. The deep tendon reflexes were active, especially on the right. There was slight weakness of the right upper extremity, with a static and an intention tremor and cogwheel rigidity on the right side. The static tremors were less pronounced and at times were absent at rest, but as soon as the child was stimulated in any way, became excited or attempted to move her right upper extremity the tremors became intense and increased in proportion to the excitement. There was pronounced ataxia in the finger to nose test on the right side. The right hand, fingers and forearm were held slightly flexed. A grasp reflex was present on the right side and a slight intention tremor on the left side. There was a definite Hoffmann sign on the left side.

The abdominal reflexes were active and equal on the two sides. An equivocal Chaddock sign was present on the left. There was a slight tremor in the right lower extremity. Bilateral ankle clonus was present, being stronger on the left side. The Babinski sign was not elicited. There was no impairment of sensation. There was hirsutism of the arms, legs and back.

The child had incontinence of the bowel and bladder at times. A provisional diagnosis was made of a space-taking lesion in the cerebrum near the midline, extending into the left frontal lobe and the basal ganglia.

The patient was examined by Dr. Alexander Silverstein, attending neurologist, who concurred with these observations but suggested that the presence of a tumor in the posterior fossa, as well as a pinealoma, should be ruled out. The patient was seen by Dr. W. H. Annesley, who confirmed the presence of bilateral choked disk.

The blood count and urinalysis gave normal results. The Wassermann reaction of the blood was negative. Roentgenograms of the skull (Dr. S. Bruck) showed separation of the suture lines, enlargement of the skull, demineralization of the posterior clinoid processes and a small area of erosion in the left frontal area. Roentgenograms of the chest showed nothing abnormal.

A ventriculogram made on December 7 showed that the left ventricle did not fill. The right ventricle showed a small amount of air, which was displaced to the right, suggesting a large lesion in the left frontal area. The fluid from the right ventricle had 10 white cells, no red cells and 40 mg. of protein per hundred cubic centimeters. The fluid from the left ventricle had 50 white cells, 3,000 red cells and 140 mg. of protein per hundred cubic centimeters. The ventricular fluid showed a slightly positive Wassermann reaction, but the colloidal gold curve was normal. (The parents' blood gave negative Wassermann reactions on two separate occasions. A spinal puncture was done on the patient three weeks after the craniotomy. The Wassermann reaction was reported to be moderately positive, and the colloidal gold curve was 1333320000. It was thought that these results represented false positive reactions, possibly secondary to an abnormal amount of protein from the tumor.)

Craniotomy was done in the left frontal area on Dec. 14, 1944, with the patient under anesthesia induced with solution of tribromoethanol U. S. P. and pentothal A huge, dusky red tumor presented through the cortex and extended to the tip of the left frontal lobe and to the midline. The tumor and brain tissue were honeycombed with cystic areas containing xanthrochromic fluid and others which showed old and recent hemorrhages. Although a large portion of the tumor could be freed from the surrounding brain tissue with finger dissection, some of the tumor extended into the ventricle and invaded the caudate nucleus.

In view of the invasive nature of the tumor and the small amount of the frontal lobe tissue remaining, a prefrontal lobectomy was done. It was impossible to know at the time of the operation whether the posterior boundary of the excision extended into the motor area; however, the excision was carried far enough posteriorly to make sure that all tumor tissue above the caudate nucleus was removed. There appeared to be tumor in the falx; accordingly, the anterior third of the sagittal sinus was ligated and this portion of the falx resected. The tumor tissue infiltrating the caudate nucleus was not disturbed because it was thought that the growth was an extensive, malignant one and that any attempt to remove this deep tissue would lead to injury to the internal capsule and paralysis on the opposite side. The dura also showed evidence of infiltration or adhesions of tumor tissue and was removed, including the area where the tumor had eroded into the left frontal bone. No attempt was made to close the dural defect with a graft. The bone flap was replaced and wired into place with stainless steel sutures and the scalp flap closed in the usual manner with interrupted silk sutures.

Dr. William Spaeth described the portion of tumor which was removed as a spherical mass of tissue, approximately 5 cm. in diameter. The tissue was soft and friable, although the mass appeared well encapsulated. At one pole a depressed area containing blood clots was seen.

Dr. E. Agerter described the histologic appearance as follows: "A section of this tumor showed a mass of tumor cells, with a very small amount of supportive tissue. Here and there were cores of fibrous stroma, carrying small blood vessels. They were covered with a layer of very tall, narrow cells, which were fusiform or goblet shaped. These cells and their pattern were typical of ependymoma."

Convalescence was stormy during the first twenty-four hours after operation, with gradual improvement to recovery.

The latest examination, made on April 18, 1946, fourteen months after operation, showed that the child was normal and happy. She had no complaints and was doing well in kindergarten. The pupils were equal and reacted well to light and in accommodation. The external ocular movements were normal. The eyegrounds showed no choking of the disks. .The visual fields were normal in the finger test. The cranial nerves were normal except for slight weakness in the lower third of the right side of the face. The tongue was protruded in the midline with no tremor.

The biceps and triceps reflexes were notably decreased on both sides. The Hoffmann sign was not elicited. There was no grasp reflex. Resistance to flexion or extension in the upper extremities was not increased, and cogwheel rigidity was not present. Tremor was entirely absent, both at rest and during volitional movement. There was no dysmetria or ataxia. Muscular power was excellent in both upper extremities. The right patellar reflex was slightly stronger than the left. Babinski, Chaddock, Oppenheim or Gonda signs were absent. There was no ankle clonus. Sensation and motor power were not impaired in any of the extremities.

Comment.—A large ependymoma involving the frontal lobe and the caudate nucleus produced contralateral classic parkinsonian-like tremor and cogwheel rigidity. Removal of the tumor and all the frontal lobe anterior to area 4 resulted in complete cessation of tremors, cogwheel rigidity and excellent motor function up to the time of this report, fourteen months after operation. The tumor tissue in the caudate nucleus was not removed. The removal of area 4 of the premotor cortex was not necessary for the relief of tremor and rigidity in this case.

I believe that the discrepancies in the results reported by various surgeons who removed the same or different areas of cerebral cortex for the relief of parkinsonian-like tremor may be due (aside from the technical factors) to the variations in the location of the cerebral lesion. Careful analysis of postoperative results in the light of the cause and location of the cerebral lesion producing parkinsonian tremor would be a more accurate surgical approach to this problem.

[The patient was presented before the society for comments and examination.]

DISCUSSION

DR. A SILVERSTEIN: Dr. Scott should be highly commended, not only for his excellent paper but, of greater importance, for the remarkable results in and his successful management of this case. He should be especially complimented on his excellent judgment at the operating table, when he decided to remove such an extensive infiltrating tumor of the brain instead of backing out, as is too frequently done in such cases.

I must question Dr. Scott's interpretation of the "parkinsonian tremor," which he accepted as a sign of involvement of the frontal lobe. He has stressed, with considerable detail, that a lesion of the frontal lobe seldom produces a parkinsonian tremor. One might add that in children, even those with encephalitis lethargica, the parkinsonian syndrome, with or without tremor, is an infrequent occurrence.

My own interpretation of the tremor in this case is quite different from Dr. Scott's. I believe that this sign should not be isolated from the rest of the clinical picture but, rather, should be considered as only one of a group of symptoms. For example, the earliest complaints of vomiting and headache were signs of increased intracranial pressure.

The positive signs, the cracked-pot sound, paralysis of upward gaze, inequality of the pupils, paralysis of the sixth nerve, signs of damage to the pyramidal tract and cerebellar dysfunction, all present bilaterally, were all evidence of compression of the brain stem, possibly with herniation through the tentorium, and generalized intracranial pressure.

In my opinion, the tremor was not the typical "parkinsonian tremor," nor was the posture of the hand of extrapyramidal type. The hand was clenched tightly, with the thumb strongly adducted in the palm of the hand. There were irregular, fairly slow jerking movements, with relatively large excursions when the hand was at rest. This tremor increased on emotional stimulation and became much more pronounced on voluntary movement, suggesting complete decomposition of movement. The tremor resembled the type seen with involvement of the red nucleus and other structures of the brain stem.

In short, I believe that the obvious signs of increased pressure, such as separation of the bones of the skull and choked disk, together with focal signs pointing to involvement of the brain stem (paralysis of upward gaze and bilateral paralysis of the sixth nerve) favor consideration of the tremor as a distant sign of compression of the brain stem rather than a focal sign of involvement of the frontal lobe.

It should also be stressed that the postoperative clinical course, with progressive improvement of the tremor, muscular rigidity and other signs, was a fairly typical result of relief of compression, such as the disappearance of paralysis following the removal of a meningioma. On the other hand, if the tremor were due to involvement of the frontal lobe, surgical ablation of the frontal lobe should have resulted in prompt cessation of the tremor, which it did not.

Dr. Scott has made a valuable contribution to the understanding of the mechanism and surgical management of tremor, and he should be encouraged to continue his particular operation in similar cases in the future. However, more research and experimental work should be done to prove that an ablation of the part of the frontal lobe which he has indicated will successfully eliminate the so-called parkinsonian tremor.

DR. FRANCIS C. FORSTER: I should like to ask Dr. Scott whether some of the suppressor areas of the cortex had been removed with the caudate nucleus. These suppressor areas have been worked out in the subhuman primate brain by Dusser de Barenne and McCullough and their colleagues, and they are known to exist in subprimate species of vertebrates. They exist in the frontal cortex, as well as in other lobes. In the frontal cortex of man, area 4-s has been demonstrated by Bucy and Garol. In your posterior approach to area 4, Dr. Scott, you would probably have encroached on area 4-s and, although it is not fair to ask whether you ablated 4-s, it is a possibility. Area 8-s may possibly have come along with

that. If you removed the caudate nucleus, you would have succeeded in removing the entire corticocaudate circuit. I wonder whether this might enter into the mechanism of the alterations you produced. These parkinsonian tremors arise from disturbing mechanisms within the circuit, and in this instance you would have removed the entire circuit.

Dr. H T. Wycis: Does Dr. Scott feel that the invasion of the caudate nucleus by the tumor was responsible for disrupting the suppressor circuit? Since areas 4-s and 8-s converge on the caudate nucleus, it is entirely possible that the suppressor circuit was also interrupted, so as to release the parapyramidal system.

With regard to the question asked by Dr. Forster, it is apparent that area 4-s was not disturbed, since in such a case spasticity would certainly have appeared.

Dr. Frederic H. Lewey: About twenty-five years ago Schuster presented a series of cases of tumors of the frontal lobe and suggested that the tremor was caused by involvement of the frontal lobe. Necropsy revealed that all the patients with tremor or other signs of parkinsonism showed actual involvement of the basal ganglia by the tumor.

Dr. Joseph C. Yaskin: The statement was made that a generalized increased intracranial pressure was responsible for the tremor in this case. I do not believe such an explanation is plausible, for one sees many children with increased intracranial pressure who do not show the parkinsonian complex. In evaluating the symptoms in this case, one should bear in mind two facts: (1) The tumor was large enough to press on the caudate nucleus, even though the latter was not invaded; and (2) there is a strong possibility, as Dr. Scott indicated, that the frontocerebellar pathways were involved and that the tremors of cerebellar origin are not always easy to differentiate from those of the extrapyramidal system.

The second suggestion by Dr. Forster was that the neurophysiologic state in children may be very different from that of the adult, and one does not see many tumors of the premotor part of the frontal lobe in children. At least, I have not. Perhaps a study of this particular group of tumors may throw more light on the symptoms in this case.

Dr. A. M. Ornsteen: In clarifying the issue, there should be definite understanding as to the presence of parkinsonian tremor. If this child had parkinsonian tremor, the discussion is justified from the standpoint of its elimination surgically. If the child had a tremor, not parkinsonian, it is a different concept. I have not heard anything yet to indicate that this child presented a parkinsonian picture. Dr. Silverstein, who saw the child, said the tremor was not parkinsonian. Dr. Scott described the tremor as of the intention type. Rarely is a parkinsonian tremor an intention tremor, except perhaps in the advanced stage. It is usually a tremor of rest. This child did not have the disease more than two months before the operation. The posture of the hand, Dr. Scott said, was not parkinsonian. Dr. Silverman described the hand as clenched, with thumb in palm. The parkinsonian picture, to accept it as a parkinsonian state, has to have hypokinesis or akinesis, spontaneous movements and rigidity. But an intention tremor with a tumor of the frontal lobe cannot be categorically classified as a parkinsonian tremor. It is best, I believe, to refer to it as a tremor due to tumor of the frontal lobe. In that case, it is easier to conceive of tremor because of the widespread connections of the extrapyramidal tracts in passing from the cortex to the basal ganglia. If Dr. Scott would agree that it is a question of tremor due to tumor of the frontal lobe, one might follow right along. If the discussion is limited to a parkinsonian tremor, the hypotheses expounded are not easily followed.

Dr. Robert A. Groff: The point was made by Dr. Ornsteen that the tremor displayed by this patient was not "parkinsonian," but simply a tremor. I wish to emphasize this, too. Some may have noticed that when I announced the title of the paper I left out the word "parkinsonian." The description of the tremor does not fit what is considered "parkinsonian."

A number of years ago Dr. Weisenburg said, after a presentation by Dr. Gibbs, of Boston, on localizing signs of cerebral function as presented in 2,000 cases of

cerebral tumor from the Cushing Clinic, that one cannot assume that the signs presented by a cerebral tumor in a particular area are the functions of that area. The factors of increased intracranial pressure and of edema surrounding the tumor must be accounted for, because they cause involvement of areas adjacent to and at a distance from the tumor. My experience has supported this statement, and I think it is dangerous to use tumor location as a basis for localization of cerebral function.

DR. MICHAEL SCOTT: I should like to clarify why I called the tremor in this case a parkinsonian tremor. The child had a constant static tremor in the right hand. When she became excited, the tremor increased in intensity, as does the classic parkinsonian tremor. In addition, there were a pronounced cogwheel rigidity on the side of the tremor and resistance to passive flexion and extension of the forearm.

There was no question in my mind about this. When the child was asked to place her finger on her nose, the tremor increased markedly. Dr. Silverstein states that it is not customary for a parkinsonian tremor to increase on motion. If the members of the society will recall, a few years ago I presented a patient with bilateral parkinsonian tremor; all agreed on the diagnosis and noted that the patient's hands would fly all over her face when she attempted to point to her nose

Therefore, I still maintain that the patient presented here had a parkinsonian tremor. However, she did not have the set facies and other signs of parkinsonism, and perhaps the term "parkinsonian" should not be used to describe a case in which not all the symptoms of parkinsonism are present. If I am wrong in my opinion as to what constitutes a parkinsonian tremor, I should like to be corrected

In reply to Dr. Forster's question, it is impossible for me to state the exact area of cortex removed. It is possible that area 4-s was injured. Dr. Yaskin and Dr. Wycis suggested that the tremors might be due to direct pressure by the tumor on the caudate nucleus. This may be so. On the other hand, Ody, in his study of a series of cases, said that contralateral parkinsonian tremor was an unusual symptom with tumors of the basal ganglia. My point is that the associated lesions of the cortex and the basal ganglia produced the tremor.

Effect of Lesions of the Optic Tract and of the Midbrain on Labyrinthine Nystagmus. DR. E. A. SPIEGEL and DR. N. P. SCALA, Washington, D. C. (by invitation).

In previous experiments (Changes in Labyrinthine Excitability with Lesions of Optic Tract and External Geniculate Body, ARCH. OPHTH. **34**:408 [Nov.Dec.] 1945), we observed that a marked difference between the nystagmus following clockwise rotation and that following counterclockwise rotation developed after lesions of the optic tract or of the external geniculate body. The duration of the postrotatory nystagmus to the side of operation increased up to three times, and the number of its jerks up to four times, the corresponding values of the nystagmus to the normal side. Our further experiments on cats demonstrate that lesion of the anterior corpus quadrigeminum also induces an increase in the number of jerks and of the duration of the postrotatory nystagmus directed toward the side of the operation This effect appears independently of the lesion of the occipital lobe. From the present study, and from our previous experiments, it is inferred that the appearance of this directional preponderance of postrotatory nystagmus is due to release of the vestibulo-ocular reflex arc from inhibitory impulses originating in homolateral parts of the retinas. This inhibition is brought about by a cortical and a subcortical apparatus. The superior colliculus is part of the latter mechanism. Thus, these experiments may contribute to an understanding of the little known function of the corpora quadrigemina. The biologic function of this inhibitory mechanism may perhaps be sought in the following direction: The ocular deviation on movements of the head is rather generally considered a

mechanism serving the preservation of a constancy of the visual field. This can be accomplished only if amplitude and speed of the ocular reaction are properly regulated. Retinal impulses checking the vestibulo-ocular reaction may play a part in such a regulation.

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Effect of Cortical Lesions on Labyrinthine Nystagmus. Dr. H. T. Wycis and Dr. E. A. Spiegel.

The influence of various unilateral cortical lesions on the ocular reactions to ten alternate clockwise and counterclockwise rotations was studied in dogs and cats. Definite effects were found after occipital or frontal lobectomy, the postrotatory nystagmus to the side of operation distinctly predominating over that to the normal side ("directional preponderance," i. e., increase in duration and number of jerks to the side of operation and/or decrease to the opposite side). The change lasted from a few days up to two weeks after complete elimination of the area striata, and five to ten days after frontal lobectomy. In a dog in which severe jacksonian convulsions developed it lasted over a period of two months. Superficial lesions of the parietal or temporal lobe had only a slight, if any, effect on the postrotatory nystagmus, while deep-reaching lesions of the temporal lobe produced a definite directional preponderance, apparently due to injury of pathways connecting the area striata with the brain stem. This may explain, at least in part, the observations of Fitzgerald and Hallpike in cases of tumor of the temporal lobe. In further experiments, retinal impulses were eliminated by transection of both optic nerves, and this operation was combined with lobectomies. After the bilateral section of the optic nerve, the duration of the postrotatory nystagmus was increased 2 to 3 times, and the number of jerks 1.4 to 7 times, the preoperative values. In this stage of increased reactivity of the vestibulo-ocular reflex arc, some dogs displayed a pronounced "after-after"-nystagmus following labyrinthine stimulation by turning, the rotation being followed first by a nystagmus in the opposite direction and then by one beating in the direction of rotation.

After elimination of the afferent impulses from the retinas, unilateral occipital lobectomy failed to produce directional preponderance, whereas unilateral frontal lobectomy, if extensive enough, was still able to induce predominance of the postrotational nystagmus to the side of the cerebral operation. Thus, the influence of the occipital lobe on the vestibulo-ocular reflex arc depends on afferent impulses from the retinas, while in the case of the frontal lobe the retinal impulses are dispensable.

DISCUSSION

Dr. B. H. Shuster (by invitation): The experimental work of Dr. Spiegel and Dr. Wycis is interesting, but its immediate clinical value is, of course, not immediately evident. Usually, only after accumulation of experimental data does the clinical application become apparent.

As I understand it, Dr. Spiegel and Dr. Wycis have concluded that there is a diminution in vestibular reaction in the animals experimented on after the visual pathways have experimentally been severed. The implication, of course, is that vision is much concerned with the vestibular reaction and that the interception of vision reduces the vestibular activity. Clinically, however, I cannot recall instances in which this was the case. Human beings vary so much in their vestibular sensitivity that it would be difficult to interpret diminution of reaction as concerned with impairment of vision. On the other hand, I have seen cases of pituitary tumor causing blindness in which the reaction to rotation was prolonged beyond the point of that which could be said to be due to vestibular hyperirritability. For instance, in the case I have in mind postrotational nystagmus of about seventy and eighty seconds was manifested as compared with the average of about twenty-five seconds. This, of course, is the opposite of what these animal experiments indicate. I interpret this prolonged reaction as due to hyperirritability of the

labyrinthine nuclei because of intracranial pressure, rather than as associated with the defect in vision resulting from pressure on the optic chiasm.

Dr. Milton Meyers: I noted that the authors did not attempt any explanation of the after-after-nystagmus. If they have any explanation, we should like to hear it.

Dr. Joseph C. Yaskin: I have four points in mind which require clarification. First, I assume that the pathway which modified the duration of nystagmus passes by the way of the midbrain to the posterior longitudinal bundle. If not, I should like to be corrected. I assume that the pathway starts in the external geniculate body and continues through the superior colliculus to the posterior longitudinal bundle.

The second point is whether or not there is any relation between the adversive fields responsible for the conjugate deviation of the head and eyes observed clinically and the modification of the nystagmus, as suggested by Dr. Wycis' work.

The third point is whether there is any experimental evidence that nystagmus is produced by lesions above the tentorium, except perhaps those of the caudal part of the third ventricle. In a recent paper, De Jong stated emphatically that one is wrong in assuming that nystagmus is rare with diseases above the tentorium. Every time I have made the diagnosis of a supratentorial lesion in the presence of nystagmus I have been wrong.

Last, would not the work of Dr. Wycis and Dr. Spiegel explain some of the phenomena which Dr. Shuster observes and on which he bases his diagnosis of a tumor of the left or the right temporal lobe? Are not the responses elicited by these authors helpful in explaining localization of lesions above the tentorium?

Dr. A. M. Ornsteen: Is it not known that retinal stimuli and the stability of the extraocular muscles are dependent on each other? This relation is suggested in the searching movements of the eyes in blind people. I am reminded of a physician in town who has progressive myopia and for the past decade has had increasing loss of vision; he is now practically blind. He did not have nystagmus ten years ago, but only last week I noticed what has happened in the past year. His eyes oscillate almost half the width of the palpebral fissures. With increasing loss of vision there is greater instability of extraocular tone and function, indicating that stability of the extraocular muscles depends on retinal impulses.

Dr. Michael Scott: Do Dr. Spiegel and Dr. Wycis feel that nystagmus or optokinetic nystagmus is of clinical value in localizing lesions of the temporal lobe?

Dr. Joseph C. Yaskin: The nystagmus Dr. Ornsteen discusses does not belong to the same category as the vestibular, or labyrinthine, type. It has long been recognized that nystagmus incident to amblyopia, appearing early or later in life, is an entirely different phenomenon from nystagmus due to disturbance of the vestibular pathways. Nystagmus may be divided into three types: (1) that belonging to disturbances of vision; (2) that belonging to disturbances of the internal ear, and (3) that belonging to disturbance of the pathways proximal to the labyrinth, and therefore hard to trace. I should like to hear Dr. Spiegel's recent views on that.

Dr. A. M. Ornsteen: I merely wanted to show with that clinical observation that a relation between retinal impulses and extraocular stability exists. This nystagmus has nothing to do with vestibular nystagmus.

Dr. E. A. Spiegel: Dr. Shuster has brought up a problem discussed frequently, namely, the relation of experimental and clinical work. One carries on animal experiments for several reasons: to study biologic phenomena and to see certain laws of nature established. But if one is a physician, one is interested in the light these experiments throw on clinical phenomena. One is perhaps justified in assuming that such primitive mechanisms as the reflexes of ocular muscles are similar in animals and in human subjects. Therefore the experimental worker tries to correlate his findings to a certain extent with clinical experience. It should not be forgotten that all Bárány's work was based on old animal experiments

which Hoegyes, a Hungarian physiologist, started and Breuer and Mach later continued.

It seemed to us that the question whether certain lobectomies produce inequality of induced nystagmus is of some clinical interest. For example, the question may arise whether a predominance of induced nystagmus to the right or to the left has localizing value. Two English authors, Fitzgerald and Hallpike, based their clinical studies on experimental work by Bauer and Leidler, Dusser de Barenne and de Kleyn, who found so-called *Nystagmusbereitschaft* to the side of hemispherectomy (*Brain* **65**:115, 1942). Fitzgerald and Hallpike translated the term as "directional preponderance of nystagmus" to the side of the cerebral lesion. They tried to apply the phenomenon to the local diagnosis of cerebral tumors. They observed it particularly with tumors of the temporal lobe. Our experiments may perhaps help in understanding their observations, since we noted definite directional preponderance only with lesions of the temporal lobe that reached close to the lateral ventricle. This experiment suggests that the "directional preponderance" observed by Fitzgerald and Hallpike with tumors of the temporal lobe was due to involvement of fiber connections of the occipital lobe with subcortical centers.

Dr. Ornsteen has raised the question whether searching movements in blind people are a special type of nystagmus. We are justified clinically, it seems to me, in differentiating labyrinthine nystagmus from that associated with amaurosis and amblyopia, as Dr. Yaskin has done. This does not preclude, of course, a relationship between these types of nystagmus, and there is a good point in Dr. Ornsteen's argument that the tonicity of the ocular muscles depends, at least partly, on impulses from the retina, and that loss of the centripetal impulses from the retina may result in disturbances in the tonicity of the ocular muscles and in overexcitability of the vestibular nuclei; these factors may play a part in the genesis of searching movements in blind persons, although other factors may be involved

Dr. Shuster has brought up a second question, namely, whether after-after-nystagmus is a labyrinthine phenomenon or whether it is due to a change in the tonicity of the ocular muscles. It is not difficult to answer this question, for this problem of after-after-nystagmus has not only an objective side, the nystagmic movements, but a subjective side, illusions of rotation. These illusions of rotation have been studied rather extensively by Fischer and Wodak, investigators well trained to observe their sensations. These illusions are rather frequently observed by normal persons. We have had occasion in the last few years to study a large number of normal persons in whom motion sickness was produced by rotation on a modified Bárány chair. We always asked them about the sensations they had after rotation. We confirmed what Wodak and Fischer already had observed, namely, that after the rotations these patients had a sensation of being rotated in the opposite direction if their eyes were closed. In some of the subjects these sensations stopped, and after a certain latent period they had a sensation that the rotation was reversed and that they were rotating in the opposite direction. These are only two phases. Some subjects, as Wodak and Fischer have described, are able to experience many more of these phases. They have described reversal of the phenomena occurring four or five times. These illusions, of course, have nothing to do with innervation of ocular muscles. The eyelids are closed, and retinal stimulation has nothing to do with it. It is a change of excitability in labyrinthine centers.

This brings me to Dr. Meyers' question, the mechanism of the after-after-nystagmus. Dr. Wycis has referred to the explanation briefly. It seems to me that it is to be sought in the following direction: Many central phenomena show periodic fluctuations; the labyrinthine nuclei also discharge periodically, and in this periodic discharge there is an alternate prevalence of direction, first to one side and then to the other. The result is alternation of direction of the postrotatory nystagmus, inducing after-after-nystagmus objectively and illusions of rotation in alternate directions subjectively. After-after-nystagmus has been observed in normal persons not only by Bárány but also by Woletz and Veits, by the latter

authors after a special type of intense rotatory stimulation. These authors even claimed that with their special type of prolonged labyrinthine stimulation they could produce the nystagmus in every subject. In our experimental animals there is an abnormal increase of this phenomenon. What are a few jerks normally become prolonged discharges if the vestibular nuclei are released from retinal inhibition

Dr. Yaskin brought up the problem of pathways. I was careful not to mention that because I did not want to make statements which later I might have to retract. So far as we have studied it, we can only say that we have followed the centripetal inhibitory pathway along the optic tract to the superior colliculus. There are of course various descending pathways from the colliculi. How far these descending pathways make their way with the posterior longitudinal bundle and how far outside, and whether they end in the vestibular nuclei directly or by intermediate neurons of the reticular substance, we can determine only by further study.

With regard to the adversive fields: Dr. Wycis has mentioned that we studied a rather large number of dogs with lesions of the various frontal areas; contrary to our expectations, lesions of area 8 failed to produce directional predominance, and combined lesions of areas 8 and 6 produced only a slight inequality of the postrotatory nystagmus. It seems a rather large lesion of the frontal lobe is necessary to obtain these phenomena.

With regard to the question whether supratentorial lesions can produce nystagmus our experiments have had no direct relation. I can only say that on stimulating the frontal areas one can produce first a deviation of the eyes and that this deviation of the eyes may be followed by rhythmic jerks, which might be similar to a nystagmus. Thus, by stimulating certain frontal areas one may produce eye jerks as part of a jacksonian convulsion. But with a lesion of a cortical area one can produce only directional predominance, not nystagmus, and an additional peripheral factor is needed to produce nystagmus. If these two factors are present —destruction of the frontal lobe and additional peripheral stimulation—prevalence of nystagmus in a certain direction may appear.

Dr. Scott asked about optokinetic nystagmus. Recent studies have shown that two types of optokinetic nystagmus must be differentiated. The first type, which Dr. Scala and I called active optokinetic nystagmus, appears when objects engaging the subject's attention move in the visual field. This is a cortical phenomenon, depending on the occipital lobe. The second type, which we called passive optokinetic nystagmus, is produced only when all objects in the visual field are moved in the same direction (ter Braak). This is a subcortical reflex, depending on the superior colliculi. Its pathway and mechanism may be related to the subcortical inhibitory mechanisms from the retina, described here, but this problem requires further study.

Dr. Henry Wycis: One of the features which distinguish the nystagmus described by Dr. Spiegel and Dr. Scala and that which Dr. Spiegel and I described is the transient effect of the cortical lesion. After cortical procedures we found that induced inequality of nystagmus persisted not longer than two weeks. This may be an important clinical fact, for if these methods are applied to the study of tumors one might be able to see this induced inequality at an early stage of the tumor. However, Fitzgerald and Hallpike observed an inequality in induced nystagmus in the caloric test with tumors of the temporal lobe at a later stage.

I might point out that there are other methods of examining the labyrinth besides the well worn methods of Bárány. We are careful to place our animals on a motor-driven chair so that we get as nearly as possible constant preoperative values of labyrinthine excitability.

It was distressing not to be able to locate the specific area of the frontal lobe which was responsible for producing an inequality of induced nystagmus. As I stated, it was only after large combined lesions that we got this inequality. Contrary to our expectations, lesions of the frontal eye fields failed to produce inequality.

Book Reviews

Human Torulosis: A Clinical, Pathological and Microbiological Study, with a Report of Thirteen Cases. By Leonard Cox and Jean C. Tolhurst, Melbourne, Australia. Price, $7.50. Pp. 149, with 67 illustrations. Melbourne, Australia: Melbourne University Press, 1946.

Torular infection is more prevalent in Australia than elsewhere, although cases have been reported from many parts of the world. The present monograph adds a number of new cases and brings the literature up to date, with 134 references. The work is a scholarly contribution, with all the facets of the disease presented for consideration. Torula can infect any part of the body. Pulmonary lesions are particularly stressed, with their resemblance to tuberculosis or tumor in the roentgenogram, and the authors state that their emphasis on the extracerebral lesions has been not because of the importance of these lesions but because of the desire on their part to fill out the gaps in knowledge of the disease.

The usual pitfalls are described—how torulas in the spinal fluid are mistaken for red blood cells, how the concurrence of pulmonary lesions and meningitis leads to the mistaken diagnosis of tuberculosis, how cultures are often discarded before the torulas have a chance to form colonies, how the long period between inoculation and clinical manifestations of the disease in animals (up to six months) renders studies of the pathogenicity somewhat tedious. They recognize torular infection as a systemic disease which becomes fatal when the nervous system is attacked, but even so there are cases of the disease with a proved duration of three to five years in which "torular collections" of large size were observed in the brain.

Torulosis is seldom suspected before examination in the laboratory. Smears from granulomas and cultures of the spinal fluid are the most common measures for diagnosis of the disease during life. Cultures of the blood and urine seldom yield the organism, and animal inoculation is too slow. The microbiologic aspects of Torula are studied in detail, with many references; but the authors have apparently not undertaken extensive studies with various strains in the hope of identifying subspecies. Also, there appears to be no great antigenicity in the various strains. The authors reach no startling conclusions, but their monograph serves to focus attention on a disease that is occasionally encountered and that should be more frequently recognized before necropsy. Unfortunately, there has been no progress made in the treatment of torulosis.

Problems in Abnormal Behavior. By Nathaniel Thornton. Price, $2. Pp. 244. Philadelphia: The Blakiston Company, 1946.

The cover jacket of this book states that the following subjects are treated in this book: psychic functions and psychologic types, mental mechanisms, the development of the sexual impulse, the nature of homosexuality, other irregularities of the sexual impulse, the question of neurosis, the question of psychosis, the scientific interpretation of dreams, the history and theory of psychoanalytic therapy, how internal secretions may affect behavior, some aspects of criminal psychology and the phenomena of epilepsy. One can guess how much "treatment" is given when one learns that the book is 5½ by 8 inches with large margins and large print, and is 244 pages in length, including 15 pages of introduction and 10 pages of index and bibliography, to say nothing of several pages of verse from such revealing sources as Viereck and the author himself.

In his introduction, the author makes a plea for a fair treatment of Freud's ideas. He asks for an open mind, but his begging and pleading for justice lead one to suspect that he is trying to convince himself. If one can learn anything

of Freud's contribution to psychiatry in this "treatment," one must certainly have read Freud's "Collected Papers" first.

This is supposed to be a book of "problems." There is no question about it. The problems are certainly posed. But the psychiatrist is not in need of a brief book like this to formulate the problems of abnormal behavior for himself, and the layman is not in need of more problems—and when the problems need solving mystic verse does not help.

Why this book was written will never be known unless as an opportunity to jump on the psychiatric bandwagon to get something published.

News and Comment

THE AMERICAN SOCIETY OF ELECTROENCEPHALOGRAPHY

The American Society of Electroencephalography will hold its first annual meeting in Atlantic City, N. J., June 13 and 14 at the Marlborough-Blenheim Hotel. The detailed program will be announced in May. The meeting will be open to all interested physicians and physiologists.

CORRECTION

In the article by Drs. Chapman, Finesinger, Jones and Cobb entitled "Measurements of Pain Sensitivity in Patients with Psychoneurosis," in the March issue (ARCH. NEUROL. & PSYCHIAT. **57**:321, 1947), the numbers on the ordinate in figures 1 and 2 should be preceded by a decimal point.